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FEBRUARY 1955
VOLUME 53 NUMBER 2

From Harrison, p. 275

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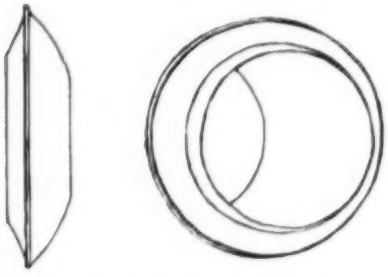

Senile monocular aphakia is not very often much of an optical problem, because the unoperated eye usually has such poor vision that the little remaining vision can be successfully inhibited by the use of a strong plus lens.

The case that is often very trying to the practitioner is the one of a traumatic cataract in one eye and excellent vision in the other. The successful extraction of the cataract results in a very real problem for the ophthalmologist as well as his patient. The operated eye will project a retinal image approximately 25% larger than the image in the unoperated eye. If corrected with ordinary lenses, binocular vision is impossible because of the difference in retinal image sizes.

Some men have tried to keep the visual acuity good in both eyes by permitting the patient to use one eye for reading and the other eye for distance. This idea, of course, was calculated to keep the eyes from deviating by maintaining good acuity in both of them. Very often, unfortunately, this method didn't work, because without fusion there was no reason for the eyes to remain straight, and there was often a noticeable deviation.

The solution to the problem of maintaining binocular fusion and undeviating eyes lies in the use of the Catmin lens. The Catmin is a minifying lens which, when used in front of the operated eye, results in approximately the same retinal image size as is inherent in the unoperated eye. The Catmin is, in effect, a Galilean telescope reversed —that is, the plus component is nearer the eye and the minus component out in front. The Catmin lens is not an experiment, having been used successfully for a great many years. In recent years, its performance has been improved by coating the two elements that are necessary for its construction. If the cataract is of long standing, it is sometimes necessary to use a prism fitover to start the patient on the road to binocular vision. Usually in a matter of weeks the binocular function can be restored and the patient will have not only good fusion but a surprising amount of depth perception.

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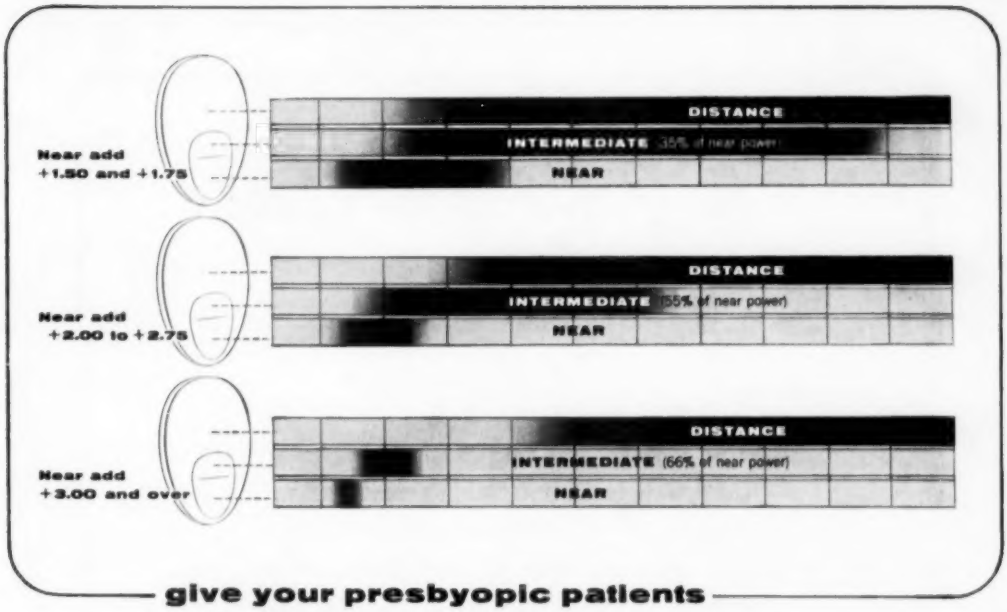

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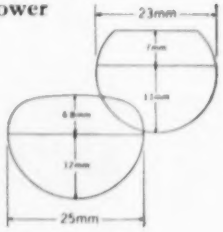

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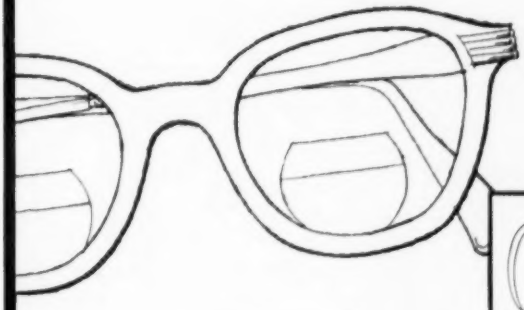

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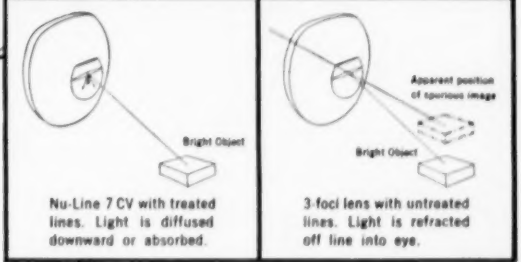

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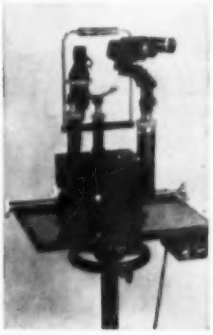

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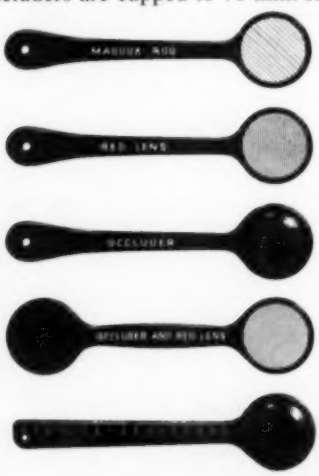

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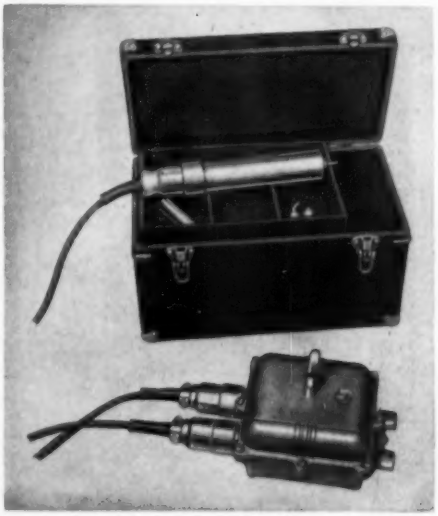

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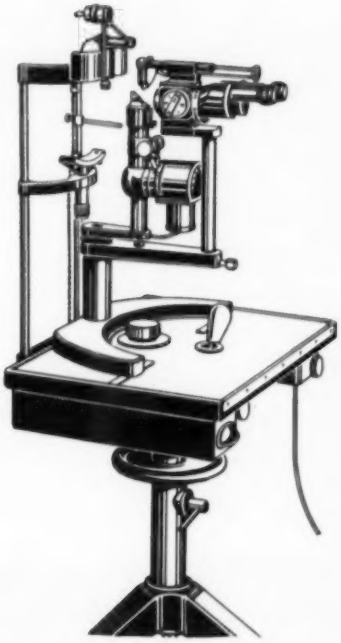

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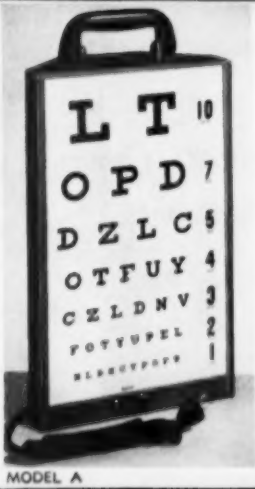

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USES AND ABUSES OF ADRENAL STEROIDS AND CORTICOTROPIN

MICHAEL J. HOGAN, M.D.
PHILLIPS THYGESON, M.D.
and (by invitation)
SAMUEL KIMURA, M.D., San Francisco

THE PROPER use of adrenal corticosteroids and corticotropin in ocular diseases has been clarified gradually, so that ophthalmologists have become aware of many of the limitations inherent in this type of therapy. The purpose of this paper is to present information obtained from the treatment of a large series with a view to establishing a therapeutic regimen in certain types of ocular lesions. A number of the ocular complications we have encountered seem to have resulted from overtreatment or from an untoward response to steroid therapy. Therefore it is deemed advisable to emphasize the nature of some lesions and to discuss the undesirable effects resulting from the injudicious use of such therapy in specific types of disease. A brief description of the characteristics of each of the hormones commonly used in ophthalmology will be given, together with a discussion of their correct and incorrect therapeutic use.

ADRENAL CORTICOSTEROIDS

Cortisone (Compound E)

Cortisone is one of a number of hormones produced by the adrenal cortex. It exerts pronounced metabolic effects, characterized by retention of sodium, chloride, and water; an increased excretion of potassium, calcium, and phosphate, and the production of a negative nitrogen balance. Neoglucogenesis as a result of formation of glucose from noncarbohydrate foods may cause a type of hyperglycemia simulating diabetes. Administration of cortisone leads to the suppression of endogenous adrenocortical secretions. Therefore, after cortisone therapy has been prolonged, one should discontinue it slowly, so that the adrenals may have the opportunity gradually to increase the endogenous supply of steroids. Any unusual post-therapeutic stress may cause severe reaction unless this biologic mechanism is fully understood.

Continued large doses of cortisone may delay the production of connective tissue cells and inhibit wound healing, though average doses, such as those used in the treatment of most ocular diseases, do not seem to interfere with healing.

Cortisone has a decided effect on the mechanism of defense; for example, patients with Addison's disease are extremely susceptible to stress of all kinds; this susceptibility can be reversed on administration of steroids. The dramatic effects of cortisone and corticotropin on the processes of inflammation are well known, and numerous studies show that the inflammatory reaction to such agents as chemical irritants, foreign proteins, and bacteria may be inhibited. It is now evident that cortisone decreases vascular permeability, with the result that there is a lowered amount of exudate. It also causes migration of inflammatory cells and increases phagocytic activity. As a result of inhibition of inflammatory reaction, the normal defense barriers do not form, and in bacterial infections the spread of micro-organisms is facilitated. Unfortunately, the signs of toxemia are also inhibited, so that the physician may be unaware of the systemic manifestations of serious infection during hormone therapy.

It is probable that corticotropin and cortisone modify or inhibit the synthesis of antibodies; this may be of significance in infectious diseases.

These studies were supported by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, Bethesda, Md.

Department of Ophthalmology and the Francis I. Proctor Foundation for Research in Ophthalmology, University of California School of Medicine (Dr. Hogan).

The following contraindications and precautions should be observed.

Contraindications to the use of adrenocortical steroids and corticotropin:

1. Peptic ulcer
2. Diabetes
3. Tuberculosis
4. Hypertension (unless mild, and the patient is constantly under observation)
5. Heart disease (unless the patient's health permits such therapy safely)
6. Infectious diseases (unless coincident antibiotic therapy is being given)

Precautions to be taken during prolonged therapy:

1. Frequent urinalysis (at least twice weekly at the onset)
2. Frequent blood pressure recordings
3. Weight measurements at weekly intervals to rule out water retention
4. Administration of potassium to replace that lost in the urine and to prevent sodium retention
5. Constant observation for evidence of sepsis or perforation of peptic ulcer
6. Watch for evidence of Cushing's syndrome
7. Careful watch for an exacerbation of the ocular inflammation

Precautions to be taken during withdrawal:

1. Reduction in the amount of hormone should be slow. Over a period of one week the hormone should be reduced each one to two days by amounts of 10 to 12.5 mg. before reaching complete withdrawal.
2. There should be constant observation for evidence of infection and evidence of stress. Any stress should be avoided.
3. Corticotropin should be given for a week, or until normal levels of cortisone secretion are restored.

Dosage and Routes of Administration.—1. Oral and Intramuscular Medication: It was shown very early that cortisone administered orally produces effects similar to those achieved when administered intramuscularly. However, its action has been found to be less permanent. A peak of plasma 17-hydroxycorticosteroids occurs one hour after oral administration and returns to normal within four to eight hours. After intramuscular administration little or no rise in plasma levels can be detected. Circulating cortisone undergoes rapid removal from the blood stream,[1] so that the absence of high levels following intramuscular administration is not surprising, considering the doses usually employed.

For oral use, 25 mg. tablets are usually employed, although tablets of 5 mg. are also available. For intramuscular administration the acetate suspension, containing 25 or 50 mg. per cubic centimeter, may be used. Effects following intramuscular administration are delayed 3 to 4 hours but persist for 24 hours. A single daily injection will usually suffice because of its prolonged effect. For an immediate effect one may resort to oral therapy or treatment by the intravenous route.[2] In the average ophthalmic case the oral method of treatment is more satisfactory, unless one is dealing with a juxtapapillary or macular lesion and an immediate effect is desirable. In such cases the intravenous use of corticotropin or specially prepared forms of cortisone may be more acceptable. Although it is rare for such an emergency to exist, in ophthalmology one should be prepared to carry out such methods of treatment.

In ophthalmic cases the usual dosage is the administration of 300 mg. the first day, 200 mg. the second day, and 100 mg. each day thereafter, depending on the reaction of the patient and subsidence of the lesion. If an immediate response does not occur, it may be necessary to increase the dose to 400 mg. to achieve a sustained therapeutic effect. The medication must be continued as long as activity of the disease indicates the vision is endangered. As the acute inflammation subsides, one may consider reducing the dose gradually. Therapy should be continued until all danger has subsided. In the treatment of cases which are chronic at the onset, one must be guided by the symptoms and signs of overdosage, plus the degree of subsidence of the inflammation. One should attempt to reduce the dose to the necessary minimum level.

In the case of excessive infectious processes involving the posterior segment, one should be alert for evidence of exacerbation

of the process during treatment. We have observed disastrous effects in several patients who were not under careful scrutiny. Oral and intramuscular cortisone therapy is now used for acute inflammatory processes in the posterior segment and for chronic anterior ocular inflammations which do not respond to topical therapy.

2. Topical Therapy: (*a*) Solutions and ointments of cortisone. Cortisone acetate suspension is provided by several manufacturers in 0.5% and 2.5% solutions for use as ophthalmic drops. Suspending agents and preservatives have been added, but only rarely do they result in allergic reactions. Free cortisone does not seem to be more effective. Cortisone ointment, 1.5%, is available for topical application. Very little difference can be detected between the effectiveness of ointments and of solutions. Ointments, however, are more difficult for the patient to administer, and therefore are less likely to be effective. Drops can be administered by the patient to the affected eye every one to two hours until a therapeutic effect is obtained. For an unknown reason, in some patients drop medication is ineffective. In such cases one may resort to subconjunctival injections before considering oral or parenteral therapy (Table 15). Subconjunctival injections of 0.3 to 0.5 cc. of 0.5% cortisone acetate suspension should be given under the conjunctiva beneath the upper lid, as far back as is possible, to prevent the solution from extending to the limbus. In cases not responding to drop medication, response to subconjunctival injections is remarkable.

(*b*) Suggested routine for topical therapy.

(1) Cortisone acetate suspension may be given as drops, 0.5% solution, every hour.

(2) Cortisone acetate ointment, 1.5%, may be applied at night.

(3) If the above treatments fail to control the inflammation, subconjunctival injection of 0.5 cc. of the 2.5% suspension of cortisone acetate every 3 to 5 days may be tried.

(4) Should the last fail also, oral or parenteral therapy may be tried.

Hydrocortisone (Compound F)

From metabolic and therapeutic standpoints hydrocortisone has effects similar to those of cortisone. That there is a difference in the potency of these two medications has been amply demonstrated. Measurements of various metabolic effects in man and animals show hydrocortisone to be considerably more potent. The difference in the local effects of these two hormones has not adequately been explained.

Hydrocortisone acetate has been found to have metabolic effects as intense as free hydrocortisone. Intramuscularly administered, hydrocortisone acetate appears to be relatively inert. Hydrocortisone is one-seventh as soluble in body fluids as cortisone, and this fact may influence its diffusion.

The same contraindications and precautions are necessary with hydrocortisone as with cortisone. It has been observed that with hydrocortisone possibly fewer effects of overdosage become apparent because of the lower dose required to achieve a therapeutic response.

Dosage and Route of Administration.—1. Oral Medication: Oral administration of hydrocortisone acetate or of the free alcohol leads to a rise of the plasma 17-hydroxycorticoids to peak levels within an hour and the gradual return to control level in four to eight hours. The ineffectiveness of intramuscular hydrocortisone acetate suspensions has already been mentioned. Acetate tablets are supplied in the 20 mg. dose form, and solution is available as 25 mg. per cubic centimeter of saline suspension. The dose on oral administration is given according to the severity of the case. Usually 80 mg. is given on the first day (in divided doses), and the dose is reduced on the second and third days in accordance with the clinical response. Only a rare ophthalmic case requires rapid and intense hormone effect. In such an instance, hydrocortisone acetate suspension containing 25 mg. per cubic centimeter may be dissolved in isotonic saline or a dextrose solution and administered intravenously. This procedure seems to be the method of choice,

because maximal and immediate metabolic effects are produced.

2. Topical Application: As there are commercial cortisone preparations, so also are there hydrocortisone acetate solutions and ointments available for topical use. The dosage and method of application are the same. The hydrocortisone free alcohol is not yet available commercially. A therapeutic study comparing the effectiveness of the free alcohol and that of the acetate on topical application has shown no difference between the two preparations. The following routine for treatment of external ocular diseases is recommended:

(*a*) Hydrocortisone acetate as drops (0.5% to 2.5% solution of the suspension) in the conjunctival sac every hour. This is to be carried out if cortisone has failed with topical and subconjunctival injections. In certain diseases, such as vernal conjunctivitis, sclerosing keratitis, and contact dermatitis of the lids, one should begin therapy with hydrocortisone drops or ointment, and in vernal conjunctivitis the 2.5% solution seems to be more effective.

(*b*) Hydrocortisone ointment, 1.5% instilled into the conjunctival sac at night.

(*c*) If this fails, subconjunctival injection of 0.3 to 0.5 cc. of the 2.5% solution beneath the upper lid.

(*d*) If this fails, oral or parenteral therapy.

Topical therapy must be reserved for diseases of the anterior ocular sergment, conjunctiva, and eyelids. Inflammation involving the region of the disc, papillomacular bundle, and macula should be treated as an emergency, by rapid oral or intravenous therapy.

Adrenocorticotropic Hormone (Corticotropin)

Adrenocorticotropic hormone (corticotropin) is produced by the pituitary gland as a response to stimuli derived from the environment, such as injuries, infections, or the necessity for unusual exertions. The corticotropin thus liberated acts on the adrenal cortex to cause increased production of a number of hormones, among which are cortisone and hydrocortisone. Therefore the effects of corticotropin are identical with those produced by these hormones. As a result, the local use of corticotropin is without effect. Corticotropin cannot be given by mouth, because the hormone is destroyed in the intestinal tract. Various methods for intramuscular and intravenous administration have been developed. Special preparations (gel forms) which undergo slow absorption and exert a more prolonged effect have been devised for intramuscular use.

With corticotropin therapy the same precautions as with cortisone are necessary.

Dosage and Routes of Administration.—1. Intramuscular Therapy: The initial dosage varies from 80 to 120 mg. a day, divided into four doses, given at six-hour intervals. As the disease responds, the dosage may be reduced to 50 to 80 mg. a day or, if no response occurs, may be increased to 100 to 150 mg. a day, the six-hour intervals of administration being always retained. There are available for intramuscular use long-acting preparations which contain corticotropin. The same dosage is appropriate, usually at 12-hour intervals, and the necessity for frequent injections is obviated. As the disease responds, the dosage is adjusted until the least amount necessary to control the inflammation is found. In case prolonged therapy becomes necessary, the long-acting preparations are preferable.

2. Intravenous Therapy: Twenty-five milligrams of corticotropin may be dissolved in a liter of 5% glucose and saline solution and given as an intravenous drip over an eight-hour period once daily. This method of administration seems to be from 8 to 12 times as effective as the intramuscular route. Larger doses (40 mg.) may be indicated in acute emergencies, but 25 mg. is adequate in most cases. After the acute process has become quiescent, the intramuscular method of treatment may be instituted.

The use of corticotropin is not advantageous in that it requires intramuscular or intravenous therapy. There are, however,

cases which do not respond to cortisone and hydrocortisone and in which corticotropin may produce a favorable therapeutic effect. Response may be delayed, however, because of the adrenocortical suppression which may have occurred in the preliminary trials with cortisone and hydrocortisone. As a result of these observations, it seems necessary to limit the use of corticotropin to treatment of chronic anterior ocular disease and to acute inflammations involving the region of the disc, papillomacular bundle, and macular or paramacular area. In the cases of acute inflammation of the posterior segment one is faced with the choice of using intravenous corticotropin or hydrocortisone. If either hormone is used judiciously, the outcome should be the same.

As a comment on the use of hormones for the treatment of disease we quote Thorn and associates [3]:

> It is clear today that they have achieved a definite area of clinical usefulness. In certain specific situations, their use may be life saving. In others they provide a nonspecific means of controlling, at least temporarily, many metabolic, inflammatory and allergic disorders. Although these agents do not provide a *biologic cure* for a single known entity, their careful but imaginative use has created numerous and effective therapeutic approaches where none had previously existed. It must be emphasized, however, that the hormones serve in no way as substitution for standard measures of supportive treatment.

Experience in the hormone therapy of a large number of diseases in ophthalmologic practice is limited; therefore we cannot draw exact conclusions for each disease. The selection of patients for oral, parenteral, or intravenous hormone therapy should be made on the basis of the severity of the disease, its likelihood of causing permanently reduced visual acuity, and the presence or absence of associated systemic disease.

Long-Term Therapy: Cases of bilateral ocular disease which will almost certainly result in severe or total loss of vision over a period of time should be treated continuously with a variety of methods and preparations in order to achieve maximum results and reduce sequelae to a minimum. There is evidence that in apparently hopeless cases such methods are advisable.[4] During the therapeutic course frequent examinations are necessary to avoid complications which may be attendant upon treatment. It is well to keep in mind that with the use of cortisone or hydrocortisone there may be no therapeutic response, though one may become manifest upon a change to corticotropin, and vice versa.

We have used these hormones for the treatment of ocular diseases since late 1949. A previous report of our experience was given in 1951.[5] At that time we emphasized the unfavorable response to hormone therapy in patients with chronic ocular disease. Two of those patients who have rheumatoid arthritis are still under treatment; in one the ocular disease has been eradicated entirely. In the other, who has been treated now for four years, except for a six-month interval of therapy with phenylbutazone (Butazolidin), the disease continues a minimal course, without obvious complication. For the purpose of this report, we have summarized our experience with cortisone, hydrocortisone, and corticotropin. An attempt has been made to compare the topical effects of cortisone and hydrocortisone. We are able to show also a small series of cases in which response to drop therapy did not occur but did occur after subconjunctival injection. These cases were studied at the University of California School of Medicine Eye Clinic and in our private practice. A large number of the private patients were studied concurrently by the three of us in an attempt to evaluate the results of therapy. Admittedly, it is difficult to establish exact standards of therapeutic response, but in our cases the following criteria have been established:

Excellent result. Prompt subsidence within 5 to 7 days of a disease which might be expected to run a course of 21 to 28 days if ordinary therapeutic methods were followed. In a number of cases in this group the disease subsided promptly, with persisting minimal lesions, requiring an additional four to five days for complete disappearance.

TABLE 1.—*Eyelid Conditions Treated with 1.5% Cortisone Ointment*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Seborrheic blepharitis	17	0	1	16
Staphylococcic blepharoconjunctivitis *	47	4	3	40
Contact dermatitis	34	19	6	9
Meibomitis with staphylococcic blepharitis	5	0	1	4
Acne rosacea blepharoconjunctivitis	11	10	0	1
Physostigmine follicular conjunctivitis	3	0	3	0
Total	117	33	14	70

* Cortisone and neomycin or cortisone and bacitracin cured most cases, but cortisone had no effect on rapidity of healing.

TABLE 2.—*Eyelid Conditions Treated with 1.5% Hydrocortisone Ointment* *

Condition	No. of Cases	Results: Excellent	Fair	Poor
Seborrheic blepharitis	16	0	0	16
Staphylococcic blepharitis	18	0	1	17
Contact dermatitis	23	19	2	2
Acne rosacea blepharoconjunctivitis	1	1	0	0
Total	58	20	3	35

* Many of these cases were those failing to respond to cortisone.

TABLE 3.—*Conjunctival Conditions Treated with Cortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Catarrhal conjunctivitis, staphylococcic	12	3	4	5
Catarrhal conjunctivitis, Koch-Weeks	2	0	1	1
Follicular (inclusion) conjunctivitis	4	1	0	3
Keratoconjunctivitis sicca	25	0	9	16
Vernal conjunctivitis	36	2	8	26
Allergic conjunctivitis	27	9	15	3
Pingueculitis	4	2	2	0
Total	110	17	39	54

TABLE 4.—*Conjunctival Conditions Treated with Hydrocortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Catarrhal conjunctivitis, staphylococcic	9	0	0	9
Follicular conjunctivitis (inclusion)	6	1	2	3
Vernal conjunctivitis	35	30	2	3
Allergic conjunctivitis	17	14	2	1
Keratoconjunctivitis sicca	9	0	0	9
Total	76	45	6	25

TABLE 5.—*Corneal Conditions Treated with Topical Cortisone, 0.5% Solution, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Marginal ulcer, staphylococcic or endogenous	62	39	20	3
Phlyctenulosis	39	33	2	4
Herpes febrilis (disciform)	8	5	0	3 (worse)
Herpes febrilis (dendritic)	34	4	4	26
Herpes zoster keratitis	6	0	4	2 (worse)
Superficial punctate keratitis	8	8	0	0
Atopic keratoconjunctivitis	7	7	0	0
Pemphigus	4	0	0	4
Recurrent erosions	7	4	1	2
Mooren's ulcer	3	0	0	3
Syphilitic interstitial keratitis	7	2	2	3
Sclerosing keratitis	13	3	6	4
Burns				
Ammonia	4	0	4	0
Lye	1	0	1	0
Thermal	2	0	2	0
Total	206	105	46	54

TABLE 6.—*Corneal Conditions Treated with Topical Hydrocortisone, 0.5% Solution, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Marginal ulcer, staphylococcic or endogenous	18	12	4	2
Phlyctenulosis	10	10	0	0
Herpes febrilis (disciform)*	8	2	0	6 (worse)
Herpes zoster keratitis	2	0	0	2
Superficial punctate keratitis	3	3	0	0
Atopic keratoconjunctivitis †	11	11	0	0
Pemphigus	3	0	0	3
Recurrent erosions	2	2	0	0
Sclerosing keratitis	13	8	4	1
Total	70	48	8	14

* Cases of dendritic herpes febrilis not treated with hydrocortisone by us. Some of these cases were treated by others and referred to us with sequelae.

† These cases are the same as those controlled with cortisone.

TABLE 7.—*Scleral Conditions Treated with Topical Cortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Diffuse episcleritis	61	30 (3.6 da)	19	12
Nodular episcleritis	15	0	1	14
Tenonitis (allergic)	1	1	0	0
Scleritis, coccidioidomycosis	1	0	0	1
Scleritis, rheumatoid	2	0	2	0
Total	80	31	22	27

TABLE 8.—*Scleral Conditions Treated with Topical Hydrocortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Diffuse episcleritis	27	19	2	6
Nodular episcleritis	17	2	1	14
Scleritis, rheumatoid	2	0	0	2
Total	46	21	3	22

TABLE 9.—*Nongranulomatous Iridocyclitis Treated with Topical Cortisone Solution, 0.5% Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Postoperative iridocyclitis	29	22	6	1
Post-traumatic iridocyclitis	10	9	1	0
Acute rheumatoid iridocyclitis	9	7	2	0
Chronic rheumatoid iridocyclitis	4	0	1	3
Acute iridocyclitis, cause unknown	91	55	32	4
Heterochromic iridocyclitis	15	0	5 (improved)	10
Total	158	93	47	18

TABLE 10.—*Nongranulomatous Iridocyclitis Treated with Topical Hydrocortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Postoperative iridocyclitis	12	8	2	2
Post-traumatic iridocyclitis	12	4	6	2
Acute rheumatoid iridocyclitis	6	6	0	0
Chronic rheumatoid iridocyclitis	4	0	3 (improved)	1
Acute iridocyclitis, cause unknown	65	43	17	5
Heterochromic iridocyclitis	13	0	7 (improved)	6
Total	112	61	35	16

TABLE 11.—*Granulomatous Iridocyclitis Treated with Topical Cortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Sarcoid	5	0	2	3
Tuberculosis (probable)	18	8	4	6
Iridocyclitis, cause unknown	37	2	22	13
Syphilitic iridocyclitis	1	1	0	0
Vogt-Koyanagi syndrome	3	0	0	3
Coccidioidomycosis	1	0	0	1 (worse)
Total	65	11	28	26

TABLE 12.—*Granulomatous Iridocyclitis Treated with Topical Hydrocortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Sarcoid *	8	2	2	4
Tuberculosis (probable)	10	3	1	6
Iridocyclitis, cause unknown *	13	3	1	9
Total	31	8	4	19

* Two cases not responding to cortisone responded.

TABLE 13.—*Chorioretinitis Treated with Topical Cortisone Solution, 0.5%, Every Hour*

Condition	No. of Cases	Results: Excellent	Fair	Poor
Chorioretinitis, cause unknown *	26	2	0	24
Harada's disease	2	0	0	2
Chorioretinitis, due to remote infection	3	1	2	0
Total	31	3	2	26

* Twelve patients were also given subconjunctival injections every three days, without effect.

TABLE 14.—*Cases Treated Systemically*

No. of Cases	Disease	Results of Treatment * with: Cortisone E	Cortisone F	Cortisone P	Hydrocortisone E	Hydrocortisone F	Hydrocortisone P	Corticotropin E	Corticotropin F	Corticotropin P
4	Pseudotumor, orbital	0	0	3	..	..	..	0	0	1
4	Progressive exophthalmos	0	0	3	..	..	..	0	1	0
1	Diffuse severe episcleritis	1	0	0	..	..	..	..	..	..
1	Interstitial keratitis	1	0	0	..	..	..	..	..	..
1	Ocular pemphigus	0	0	1	..	..	..	..	..	..
1	Erythema multiforme	1	0	0	..	..	..	..	..	..
1	Herpes zoster	0	0	1	..	..	..	..	..	..
6	Acute iridocyclitis	6	0	0	..	..	..	..	..	..
1	Vernal conjunctivitis †	1	0	0	..	..	..	..	..	..
16	Optic neuritis	1	2	9	1	0	1	1	0	1
25	Chorioretinitis ‡	10	1	6	2	1	0	2	0	3
3	Sympathetic ophthalmia	2	0	1	..	..	..	..	..	..
4	Harada's Disease; Vogt-Koyanagi syndrome	2	0	1	..	..	..	0	0	1
21	Chronic iridocyclitis	3	2	9	1	1	0	1	0	4
89	Total	28	5	34	4	2	1	4	1	10

* E = excellent; F, fair; P, poor.
† Now carried well on topical hydrocortisone therapy.
‡ These cases are selected and probably are of mostly nongranulomatous type.

TABLE 15.—*Cases Responding to Subconjunctival Cortisone or Hydrocortisone After Failure of Drop Therapy*

Disease	Failed with	No. of Cases	Responded to	No. of Injections
Post-traumatic iridocyclitis	Cortisone drops	1	Cortisone	4
Acute rheumatoid iridocyclitis	Cortisone drops	2	Cortisone	4
Acute iridocyclitis, cause unknown	Cortisone,	4	Cortisone,	3
	Hydrocortisone	1	Hydrocortisone	2
Episcleritis, diffuse	Cortisone	2	Cortisone	5
Total.....		10		

Fair result. Fairly prompt subsidence (within 10 days) of the intensity of inflammation, followed by slow disappearance (which ordinarily might require 21 to 28 days) within an additional 5 to 7 days.

Poor result. Only slight diminution of the external inflammatory reaction, with no significant tendency toward the disappearance of the inflammatory process.

The results of treatment of 989 cases of eye conditions by topical cortisone and hydrocortisone drops or subconjunctival injections and of treatment of 90 cases by systemic medication are given in Tables 1 to 15.*

COMMENT

Topical Therapy.—The treatment of certain dermatoses of the eyelids with ointments containing cortisone and hydrocortisone has shown that hydrocortisone is the more effective in the control of urticaria, drug eruptions, and contact dermatoses of plant and chemical origin. For acute contact dermatitis secondary to the use of cosmetics, or due to other contactants of plant or chemical origin, 1% to 2.5% hydrocortisone in a water-soluble base, such as polyethylene glycol (Carbowax), is extremely satisfactory. The blepharoconjunctivitis of acne rosacea responds well to topical therapy with cortisone, hydrocortisone drops, and ointments.† Our experience with this condition confirms these observations.

Because of the frequently associated staphylococcic infection, we feel there is a definite place for the use of combinations of topical cortisone or hydrocortisone with antibiotics in infectious eczematoid dermatitis, contact dermatitis, phlyctenulosis, acne rosacea, and catarrhal ulcers of the cornea.

In our experience, vernal conjunctivitis has responded poorly to topical application of solutions and ointments of cortisone. However, similar preparations of hydrocortisone were remarkable for their effect upon this condition. Symptoms were relieved almost immediately, and relief was maintained as long as therapy was continued, but relapses were invariable upon discontinuance of therapy. Examination of the papillae and the conjunctiva showed some reduction in hyperemia, discharge, epithelial keratitis, and thickening, but papillae persisted. The elevated lesions of limbal vernal conjunctivitis gradually disappeared. These observations parallel those of Gordon and McDonald.‡

Cases of keratoconjunctivitis sicca failed to respond to topical cortisone or hydrocortisone therapy in all instances. Three cases have been treated with cortisone by mouth, with good improvement, but all were instances of severe Sjögren's syndrome, and the improvement may have been due to a generally improved nutritional status. Fitzgerald,[8] Duke-Elder,[9] Frenkel[13] and Sjögren[14] (4 cases) found no improvement with corticotropin or cortisone therapy in keratoconjunctivitis sicca.

Herpes simplex infections of the cornea have been shown to respond poorly to cortisone and hydrocortisone, except for a few

* Part of the supply of cortisone and hydrocortisone used topically was furnished through Dr. Elmer Alpert, of Merck & Company, Inc., and Dr. H. F. Hailman, of The Upjohn Company.

† References 6 through 9.

‡ References 10 and 11.

cases, in which good response was obtained. It is well known that certain dendritic ulcers heal spontaneously within 7 to 10 days (usually 2 to 3 weeks); therefore the subsidence of such ulcers in a few reported cases must not be taken as evidence of a specific cure. Generally, poor results have been observed in cases of dendritic ulcer of the cornea treated with either cortisone and hydrocortisone. In a previous report,[12] we emphasized the lack of response in 13 cases and observed that in 2 cases the disease became unusually severe with treatment. During the past year we have observed five cases of dendritic ulcer treated with hydrocortisone drops. In each instance a rapidly developing disciform keratitis with necrosis has occurred, and in three cases there has been perforation of the cornea. Moser [15] described two cases of herpes of the cornea, three cases of Fuchs's dystrophy, and one case in which iridectomy had been performed; in all cases severe ulcerative corneal reactions developed after topical therapy. In one case the disease was bilateral.

We would urge extreme caution in the treatment of herpetic lesions of the cornea with cortisone or hydrocortisone. The analgesic effect of cortisone causes patients to continue use of this medication topically, and the development of corneal ulcers is the eventual result.

We have observed six instances of the development of dendritic ulcers in the corneas of patients receiving topical medication for lid or conjunctival conditions. Presumably, the infection of the lid and conjunctiva acts as a trigger mechanism; the cortisone or hydrocortisone, as the catalyst. Two patients under systemic treatment with hydrocortisone for another disease have developed severe dendritic keratitis.

It is interesting to note that once necrosis begins in the disciform keratitis in such cases, vascularization from all around the limbus becomes rapidly progressive and may continue in spite of intensive steroid therapy. Such reactions were seen very rarely in the presteroid era, and in most such cases a secondary infection could be demonstrated. In two of our cases secondary invading organisms could be demonstrated. In these the patients had been receiving antibiotics also. In one case a Candida infection developed, and in the other a Hemophilus infection of the herpetic ulcer, with necrosis and perforation.

Our results in the treatment of marginal corneal ulcers continue unchanged since our report of 1952.[12]

In recurrent corneal erosions treated with hydrocortisone, our results have been consistently better than in those treated with cortisone. In cases treated with cortisone a relapse has tended to occur soon after healing was established. With hydrocortisone, however, the effects have appeared to be more permanent.

The response of corneal lesions to hydrocortisone in superficial punctate keratitis has been consistly good. Though recurrences are frequent, the patients are entirely comfortable when treatment has been established.

One patient with a corneal ulcer resembling a Mooren ulcer obtained an excellent response to cortisone drops. Subsequently, he was found to have a diplobacillary infection, but this lesion cleared entirely in spite of continuance of therapy without the use of a specific antibiotic.

The seven cases of atopic keratoconjunctivitis include five which have been previously reported.[16] In all these cases remarkable remissions followed the topical use of cortisone and hydrocortisone. In five patients there has been no relapse.

In general, patients with sclerosing keratitis did better with local hydrocortisone therapy than with cortisone, and relapses were fewer. Duke-Elder [9] found a good response to topical cortisone, but found also that relapses were common.

Many patients in our series who had diffuse episcleritis improved rather rapidly with topical cortisone and hydrocortisone, but nodular episcleritis failed to respond to either hormone. Hobbs,[20] Hobbs and Ashton,[21] and Mundy [22] found that the nodule of rheumatoid disease subsided with cortisone therapy. Two patients in our series with

diffuse episcleritis responded to subconjunctival cortisone, but none with the nodular forms responded.

Our results in cases of iridocyclitis correspond closely to those of a previously reported large series.§ Post-traumatic and postoperative forms of iridocyclitis responded rapidly to the local application of cortisone and hydrocortisone. Heterochromic iridocyclitis responds poorly to local applications in drop form or to subconjunctival injections. A total of 30 observations have been made in such cases, and in our own series, of 13, there was but little response. Rheumatoid forms of iridocyclitis respond rapidly, although in two cases subconjunctival injections were required before the effect was obtained. Topical therapy of acute iridocyclitis with cortisone and hydrocortisone is satisfactory. We cannot say the same applies in chronic and granulomatous cases. However, in view of the report of Quinn and Wolfson,[4] we are reviewing a series of cases for prolonged therapy.

Systemic Therapy.—We have had disappointing results in the systemic treatment of patients with optic neuritis. Twelve cases were treated with the hormones under discussion, and in only three was what might be termed an excellent result obtained. While under treatment for the orginal inflammation, two patients developed the disease in the opposite eye.

Only those cases of chorioretinitis with lesions in a vital area were selected for steroid therapy. Ten of 19 cases treated showed an excellent response to treatment. Of three cases of sympathetic ophthalmia treated, one failed to respond completely, even with large doses of corticotropin, followed by cortisone. In one case of Harada's disease bilateral detachments developed, but responded very promptly to cortisone therapy. After two additional weeks of therapy the drug was discontinued, and a relapse occurred promptly. Therapy was begun again, with equally prompt response. After two additional weeks therapy was gradually diminished and a relapse did not occur.

In view of the experimental studies of Woods and Wood [23] in tuberculous and brucellar uveitis, one must approach the therapy of large chorioretinal inflammations with extreme caution. Every patient treated systemically with adrenocortical steroids or corticotropin should be observed daily, or twice daily, for evidence of intensification of the disease process. One such patient treated by us developed a severe reaction in the eye within 24 hours after receiving corticotropin intravenously. In two other patients severe reactions to oral cortisone therapy developed and, as a result, all vision was lost. The possibility that a fair number of cases of chorioretinal inflammations may be due to Toxoplasma also suggests that one should approach such therapy with caution. The liberation of parasites from pseudocysts could lead to exacerbations or reactivation of latent disease.

One should also examine patients under steroid therapy for evidence of secondary glaucoma. It is well known that both cortisone and corticotropin have a desirable effect in the control of glaucoma secondary to acute iridocyclitis.‖ In two of our cases (one previously reported) secondary glaucoma developed during steroid therapy. This subsided promptly on cessation of treatment. Reduction in tension did not seem to be related to exacerbation of the intraocular inflammation.

Our patients with progressive exophthalmos did not respond to cortisone or corticotropin therapy, although our dose was not as large as that reported by Kinsell.[26] These authors achieved marked reduction in the exophthalmos by the use of combined corticotropin (intravenous) and cortisone or hydrocortisone. Our results are somewhat at variance with those of Woods [19] and Cole,[27] who found a marked effect on the exophthalmos after treatment with corticotropin.

It is interesting that in three cases of orbital pseudotumor an inflammatory process failed to respond to corticotropin or cortisone

§ Duke-Elder and others.[9] References 17 through 19.

‖ References 24 and 25.

therapy. It is possible that the dose was insufficient or that treatment was not continued for a sufficient length of time.

SUMMARY AND CONCLUSIONS

A review of the principal physiologic effects of cortisone, hydrocortisone, and corticotropin is given.

Contraindications for use of these hormones are enumerated. Precautions necessary during such hormone therapy, especially during prolonged therapy, are outlined. Precautions imperative during withdrawal of the adrenal corticosteroids and corticotropin are discussed.

Dosage, preparations, and route of administration for each hormone are given. Cortisone and hydrocortisone are preferred for topical application in treatment of diseases of the skin of the lids, conjunctival diseases, and inflammation of the anterior segment of the eye. The ease of application, relatively low cost, and equal effectiveness on topical use make this method of treatment more desirable. Subconjunctival injection occasionally causes subsidence of a lesion which has not responded to drop or topical therapy. Oral administration of cortisone or hydrocortisone is preferred in acute inflammations of the posterior segment. Ease of administration makes these drugs preferable to corticotropin. In cases in which response does not occur, one may resort to corticotropin. For rapid therapy in urgent cases one should administer hydrocortisone or corticotropin intravenously, and use oral medication after suitable therapeutic response.

The results of treatment with topically administered cortisone and hydrocortisone drops or subconjunctival injections in 989 cases and with systemic medication in 90 cases are given. The therapeutic effect of hydrocortisone was found to be superior in the following conditions: contact dermatitis of the lids; vernal conjunctivitis; sclerosing keratitis; superficial punctate keratitis; recurrent corneal erosions, and diffuse episcleritis. Most other lid and anterior segment diseases responded equally well to either cortisone or hydrocortisone. No difference in effect could be detected between the cortisone acetate and the hydrocortisone acetate suspensions. Hydrocortisone free alcohol seemed to be as effective as the acetate form.

An increased incidence of dendritic ulcers (five cases) of the cornea has been found in patients treated for other conditions with local steroids.

An increased incidence of acute disciform keratitis, with necrosis, ulceration, and perforation, has been noted since the advent of topical adrenocorticosteroid therapy, and warning against its overuse is given. Results in five cases are reported.

In general, results of topical cortisone and hydrocortisone therapy compare favorably with those reported in other large series of cases of ophthalmologic disorders during the past four years. Satisfactory response occurs in the following diseases: acute iridocyclitis of all types; acute keratitis of nonviral etiology; acute conjunctivitis due to allergy; vernal type conjunctivitis; phlyctenulosis; acne rosacea, and diffuse episcleritis.

It is cautioned that oral and parenteral therapy with cortisone, hydrocortisone, and corticotropin should be reserved for acute chorioretinal inflammations adjacent to a vital area in the retina near the macula, papillomacular bundle, or disc. Intensive therapy was given in such cases, with satisfactory results. Favorable results were obtained in patients with chorioretinitis, sympathetic ophthalmia, and Harada's disease. Unfavorable results were observed in cases of retrobulbar neuritis, chronic irridocyclitis and chorioretinitis, orbital pseudotumor, and progressive exophthalmos.

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LONG-LASTING LOCAL ANESTHETIC AGENTS IN OPHTHALMIC SURGERY

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THIS PAPER presents certain experimental and clinical observations on the ophthalmologic use of two new long-lasting anesthetic agents, efocaine and U-0045.* The duration of anesthesia and local tissue toxicity produced by these new agents were compared with those produced by such widely used local anesthetics as procaine, tetracaine (Pontocaine), and lidocaine (Xylocaine). Conclusions based on the use of U-0045 to obtain retrobulbar anesthesia in more than 550 operations upon the eyeball or extraocular muscles are presented.

The advantages which would accrue from local anesthesia of sufficient duration to avoid postoperative pain are obvious. Nearly all patients have some discomfort, often severe, after intraocular surgery. Pain may cause patients to become apprehensive and restless. They may squeeze their eyelids forcibly together beneath the dressings and thus interfere with re-formation of the anterior chamber. Iris prolapse may result. Nausea and vomiting may be precipitated by ocular pain through the vagus reflex. The majority of patients require postoperative sedatives and analgesics, which may, in older people, lead to a confused mental state, hypotension, and other undesirable sequelae. Opiates, if given, contribute to nausea and vomiting.

A local anesthesia with an effect of 8 to 10 hours would eliminate most of these difficulties, because pain following ocular surgery usually begins within 1 or 2 hours after operation, when the effect of procaine begins to wear off, and diminishes or disappears 7 or 8 hours later. After this immediate postoperative period, little discomfort occurs unless complications ensue.

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* Designated U-0045, product of Upjohn Company, Kalamazoo, Mich.; not yet commercially available.

I. REVIEW OF LITERATURE

Numerous previous attempts to develop a local anesthetic with a prolonged action have been made. Procaine hydrochloride (Fig. 1 *B*) is effective for one to two hours. The duration can be increased by adding to the length of the carbon chain (Fig. 1 *C*), but the toxicity likewise increases markedly, to render this approach impractical. Crile [1] tried combinations of quinine and urea, without success. Capelle [2] employed continuous injections of procaine. Yeomans and others † reported favorable results with solutions of procaine in oil, but their use has been largely discredited.‡ Studies by Duncan and Jarvis [17] and Kelly [18] demonstrated that the prolonged anesthetic effect was caused by degeneration of the nerves brought about by the benzyl alcohol used in the solution. Abscesses, foreign body reactions, and necrosis due to anesthetics in oil were reported by Smith,[19] Emery and Matthews,[20] and Brown.[11]

Recently, Efocaine, which embodies a new approach to prolonged local anesthesia, was introduced for clinical use.[21] This preparation consists of procaine, procaine hydrochloride, and butyl-*o*-aminobenzoate in a vehicle composed of polyethylene glycol, propylene glycol, and water (with sodium meta-bisulfite and phenylmercuric borate as preservatives). Procaine and butyl-*o*-aminobenzoate are crystalline, slowly absorbable substances which are insoluble in water, but readily soluble in the vehicle used in Efocaine.

† References 3 through 9.

‡ References 10 through 16.

The resulting solution is such that when it is contaminated by body fluids or water, the anesthetic agents precipitate to form a relatively insoluble depot which remains in the tissues for one or two weeks. Anesthetic activity is retained for this period.

Enthusiastic reports on the use of Efocaine have appeared in the recent literature.§ It has been reported to be of value in controlling pain following proctologic and thoracic surgery. Weinberg ‖ reported that Efocaine produced mild necrosis, occurring in the first few days after the injection, but without permanent damage. No definite neurohistologic alterations were apparent, although fat necrosis did occur in surrounding tissues. A foreign body reaction was not produced. Reports have begun to appear in the literature,

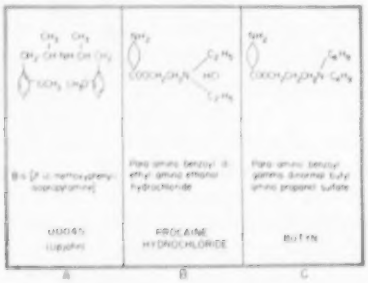


Fig. 1.—Chemical components of U-0045, procaine, and butacaine (Butyn).

however, which indicate that Efocaine not only is a highly irritable substance but is of questionable value as an anesthetic agent.¶ Perirectal sloughs, persistent neuralgia, motor paralysis of the lower extremities, and atonic bladder have followed its use. One death was caused by transverse myelitis due to an intercostal block.

Margolis and associates [38] observed the effect of Efocaine, Efocaine solvent, 80% propylene glycol, and procaine hydrochloride in rats, dogs, and rabbits. The injection of procaine intramuscularly caused no ill effect, but the other three substances produced severe muscular twitching, which lasted for about 90 seconds. This was followed by total loss of muscular irritability. Studies of microscopic sections of the injected muscles demonstrated marked necrosis. Efocaine, Efocaine solvent, and propylene glycol, when in the form of perineural injections, produced initial paralysis in about 50% of the animals. Of those given injections of Efocaine or the solvent, 20% showed some degree of paralysis after 17 days. Damage to the nerve was found in over half of the animals which were tested.

Mannheimer and co-workers,[39] after observing symptoms of local irritation following the use of Efocaine, conducted studies to determine its mode of action of effects on tissues. They found that Efocaine and the vehicle used to prepare Efocaine caused necrosis of both muscle and nerve tissues at the site of injection. They concluded that anesthesia was produced by nerve destruction.

In a recent editorial in *The Journal of the American Medical Association* [40] reviewing the effects of Efocaine, the conclusion was made that "Efocaine like alcohol acts by destruction of afferent nerves rather than like procaine by blocking afferent impulses. . . . Many have discontinued its use, and in the best interests of patients continued use of the present formula does not seem justified."

Recently, bis-[β-(*o*-methoxyphenyl)-isopropyl]-amine (U-0045) (Fig. 1 *A*) has been introduced for use in local anesthesia. This anesthetic agent consists of two molecules of the proprietary bronchodilator substance Orthoxin, joined by a nitrogen bond. The new anesthetic agent is highly potent and is available as a free base (U-0045) or the lactate salt (U-0045 lactate). U-0045 differs in chemical structure from most local anesthetics in that it is a secondary amine without an ester linkage. This structure renders it less susceptible to hydrolysis and gives it more prolonged anesthetic properties. U-0045 is a clear, colorless, fat-soluble liquid,

§ References 22 through 31.

‖ Weinberg, T.: A Study of the Effects of Efocaine upon Nerves, Muscles, Skin, and Subcutaneous Tissue, Department of Laboratories, Sinai Hospital of Baltimore, 1951.

¶ References 32 through 37.

boiling at 194 C at 1.5 mm. Hg. It has a specific gravity of 1.0234 at 27 C.

U-0045 lactate occurs as a white crystalline material, m. p. 140 to 142 C., stable in air and in solution. Although its water solubility is approximately 5%, solutions only up to 0.05% strength can be made in isotonic saline because higher concentrations cause precipitation of the hydrochloride salt. It is soluble in alcohol, but less soluble in most other organic solvents. Bass and Schroeder # have extensively studied their pharmacologic and anesthetic properties. They found that U-0045 lactate was 40 to 50 times as active an anesthetic agent as is procaine and 200 times as active as cocaine, but 4 times as toxic as procaine. In view of the greater activity, it has a therapeutic advantage of nearly 12 times that of procaine and could, therefore, be used with safety. Large amounts of methoxyphenamine can cause a fall in blood pressure.

Bass and Schroeder also found that surface applications of a 0.01% solution of U-0045 to the cornea of rabbits produced an anesthesia with an average duration of 18.6 minutes, as compared with 22.5 minutes for 2.0% cocaine hydrochloride. Stronger solutions of U-0045, up to 0.5%, were effective for as long as 240 minutes. A 0.5% solution caused some irritation, but a 0.3% solution did not. The results were similar in the guinea pig and the dog, indicating that U-0045 lactate was approximately 100 times as active as cocaine. U-0045 used in 0.5% ointments produced an anesthesia with an average duration of three and one-half hours, as compared with 1.5% U-0045 lactate, which was effective for an average duration of one and one-half hours. Neither produced corneal injury. Bass and Schroeder therefore felt that the strong anesthetic properties of U-0045 and U-0045 lactate and the absence of irritant effects furnished these compounds with sufficient promise to warrant further careful clinical evaluation.

Table I

DURATION OF ANESTHESIA

(Retrobulbar Injection of 0.5 cc Anesthetic Solution in Rabbits)

EYE	PONTOCAINE 0.1 %	PONTOCAINE 0.1% + HYALURONIDASE	XYLOCAINE 1.0%	XYLOCAINE 1.0% + HYALURONIDASE	PROCAINE HYDROCHLORIDE 2.0%	PROCAINE HYDROCHLORIDE 2.0% + HYALURONIDASE	U0045 LACTATE 0.2 %	U0045 LACTATE 0.2% + HYALURONIDASE	EFOCAINE
1	75 min.	60 min.	15 min	30 min	60 min	45 min	180 min	300 min	2 days (died)
2	105	105	60	30	105	45	240	270	17 days (died)
3	105	45	30	60	45	30	180	120	11 days
4	45	30	60	75	90	30	240	390	35 days
5	75	105	45	45	45	15	720	90	17 days
6	75	60	45	30	45	45	240	270	13 days
7	120	105	60	30	45	30	300	120	
8	90	90	45	45	30	45	540	300	
9	30	45	60	60	105	60	240	600	
10	105	105	30	30	45	30	240	120	
AVER	82	75	45	43	61	37	312	258	

We believed that Efocaine and U-0045 should be investigated for their possible usefulness in ocular surgery. The following experimental and clinical studies were performed to evaluate the anesthetic and irritative properties of these substances in comparison with certain other widely used anesthetic agents.

II. EXPERIMENTAL OBSERVATIONS

A. Duration of Anesthesia Following Retrobulbar Injections of Anesthetic Solu-

Bass and Schroeder.[41] Personal communication to authors.

tions in Rabbits.—Experiments were conducted to compare the duration of the anesthetic action of tetracaine, lidocaine, procaine hydrochloride, U-0045 lactate, each with and without hyaluronidase,* and Efocaine, following retrobulbar injection to block the ciliary ganglion and/or the ciliary nerves (Table 1). The block was considered to be successful when the pupil of the injected eye became widely dilated and fixed to light and the cornea became anesthetic. The pupillary motility and corneal sensation were then evaluated at 15-minute intervals for two hours, and then every 30 minutes. We soon found that it was easier and more dependable to evaluate pupillary light reaction than corneal anesthesia in animals. We therefore relied entirely upon that sign for determining the duration of the block. Fully grown albino rabbits were used in all experiments.

1. Tetracaine: Retrobulbar anesthesia was obtained from the orbital injection of 0.5 cc. of 0.1% tetracaine hydrichloride in 10 rabbits. Successful block resulted in all animals, the average duration of which was 82 minutes. No visible reaction resulted.

2. Tetracaine with Hyaluronidase: When the tetracaine was injected with 3 units of hyaluronidase, complete block with iridoplegia resulted in all of the 10 eyes. The average duration of anesthesia was 75 minutes, the extremes being 30 and 105 minutes.

3. Lidocaine: Retrobulbar anesthesia was obtained in 10 rabbit eyes using 0.5 cc. of 1% lidocaine. Thirteen rabbit eyes had to be injected to obtain iridoplegia in 10. The average duration of anesthesia was 45 minutes, the extremes being 15 and 60 minutes (Table 1).

4. Lidocaine with Hyaluronidase: Five-tenths cubic centimeter of 1% lidocaine containing 3 units of hyaluronidase was injected into the muscle cone of 13 rabbit eyes, resulting in complete iridoplegia in all 10 eyes. The average duration of anesthesia was 82 minutes, the extremes being 30 and 120 minutes.

5. Procaine Hydrochloride: Five-tenths cubic centimeter of 2.0% procaine hydrochloride was injected into the muscle cone of 10 rabbit eyes. A dilated fixed pupil resulted almost immediately in all instances. The average duration of anesthesia was 61 minutes, the extremes being 30 and 105 minutes (Table 1).

6. Procaine Hydrochloride with Hyaluronidase: Five-tenths cubic centimeter of 2.0% procaine hydrochloride with 3 units of hyaluronidase, injected into the muscle cone of 10 eyes, caused immediate iridoplegia in all instances. The duration of the anesthesia was less than when procaine alone was used. Pupillary reaction returned in eight eyes in 30 minutes, and in the other two in 45 minutes (Table 1). The average duration was 37 minutes. The shorter duration when procaine was mixed with hyaluronidase was probably due to the rapid diffusion of the anesthetic solution and prompter elimination from the tissues.

7. U-0045 Lactate: Retrobulbar anesthesia was obtained in 10 rabbits using 0.5 cc. of 0.2% U-0045 lactate. Eighteen eyes had to be injected to obtain iridoplegia in 10. The difficulty of obtaining ciliary nerve blocks by the retrobulbar injection of U-0045 seemed to be best explained by assuming that U-0045 diffused through the tissues very poorly and, as a result, had to be almost perfectly placed in the area of the nerves. The duration of anesthesia varied from 180 to 720 minutes. The average length of time was 312 minutes, a much longer effect than after injection of procaine (Table 1). There was no undue reaction from the injection at any time (Fig. 2 *A*).

8. U-0045 Lactate with Hyaluronidase: Five-tenths cubic centimeter of 0.2% U-0045 lactate containing 3 units of hyaluronidase was injected into the muscle cone of another series of animals. Complete iridoplegia was obtained in 10 of 11 eyes, as compared with the low percentage of successful blocks with U-0045 alone. This lends support to the claims of Atkinson and others as to the spreading action of hyaluronidase. However,

* Wydase, Wyeth, Inc., Philadelphia.

the duration of anesthesia was slightly less than with U-0045 alone. Anesthesia lasted from 90 to 600 minutes, the average being 258 minutes (Table 1).

9. Efocaine: Five-tenths cubic centimeter was injected into the muscle cone of 19 eyes. Block of the ciliary nerves occurred in only six eyes. Two rabbits died, one after 2 days and one after 17 days (Table 1). In each animal the pupils were still dilated at the time of death. The duration of anesthesia

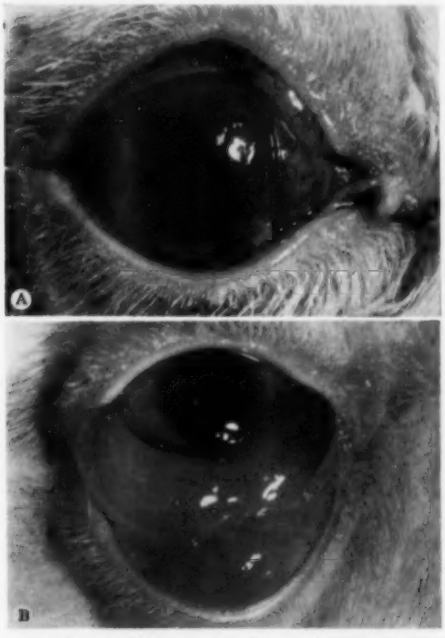


Fig. 2.—*A*, rabbit eye four hours after retrobulbar injection of 0.2% U-0045, showing no undue reaction.
B, rabbit eye four hours after retrobulbar injection of Efocaine, showing severe inflammatory reaction.

was over 10 days in all instances. Retrobulbar injection of Efocaine caused rather marked tissue reaction, manifested by pronounced conjunctival edema and chemosis, which lasted from 4 to 10 days, as well as some proptosis (Fig. 2 *B*).

Conclusions: Observations in rabbits indicated that procaine hydrochloride maintained an effect after retrobulbar anesthesia for an average of 61 minutes, while U-0045 lactate was effective for 312 minutes, tetracaine hydrochloride for 82 minutes, lidocaine hydrochloride for 45 minutes, and Efocaine for two weeks or longer. Procaine, lidocaine, and tetracaine apparently diffuse through the tissues rather well, as indicated by the uniformity of retrobulbar anesthesia which was produced in nearly all instances. Pooling of methoxyphenamine lactate in the tissues was indicated by the less uniform results following injection. Thus, 18 eyes had to be injected in order to obtain retrobulbar anesthesia in 10. Hyaluronidase seemed to increase the diffusion of U-0045 lactate. A higher percentage of successful retrobulbar injections was obtained when hyaluronidase was added, but the duration of anesthetic action was reduced. This could probably be attributed to more rapid elimination from the tissues. The average duration of anesthesia with U-0045 alone was reduced to 258 minutes. Efocaine showed even less ability to diffuse into tissues, as evidenced by the necessity of injecting 19 eyes to obtain retrobulbar anesthesia in 6. This result was to be expected because of the very nature of Efocaine. This solution is at a critical saturation level, and the anesthetic base precipitates out into insoluble form when it comes into contact with tissue fluids. The anesthetic effect of Efocaine persisted much longer than that of any of the other anesthetics, but it caused extremely severe inflammatory reactions, manifested by proptosis and chemosis (Fig. 2 *B*).

B. Local Tissue Reactions Resulting from Injection of Anesthetic Solutions in Rabbits.—Studies were undertaken to compare the local toxicity of Efocaine with that of U-0045 and with those of procaine, lidocaine, and tetracaine. Control studies had revealed that injections of solutions of isotonic saline, 2% procaine hydrochloride, 0.1% tetracaine hydrochloride, and 1.0% lidocaine caused little or no reaction when placed subconjunctivally, intracorneally, or within the anterior chamber. U-0045 and Efocaine, however, produced definite signs of tissue irritation, as indicated by the following observations:

1. Subconjunctival Injections: (*a*) U-0045 lactate. One-tenth cubic centimeter of 0.2%

U-0045 lactate was injected in 11 rabbit eyes. Conjunctival hyperemia occurred in all the eyes. Slight chemosis and edema of the conjunctiva, which lasted from one to two days, were seen in seven eyes. Three eyes required four days to return to normal.

(*b*) Efocaine. Subconjunctival injection of Efocaine caused marked conjunctival edema and chemosis, which persisted for a week or more in each of the seven eyes. Immediately after the injection an opaque deposit of procaine crystals could be seen at the site of the injection. In three animals an associated irritative iritis developed, which required 4 to 11 days to subside. The cornea in one eye became diffusely hazy but cleared in 10 days. Small localized corneal opacities adjacent to the subconjunctival injection occurred in two eyes, but these cleared on the sixth and ninth days respectively, following injection. The opaque deposit cleared in three animals by the 13th day. One conjunctival opacity lasted 12 days, and one lasted 17 days. One eye after three weeks was completely normal except for a 3 mm. corneal opacity.

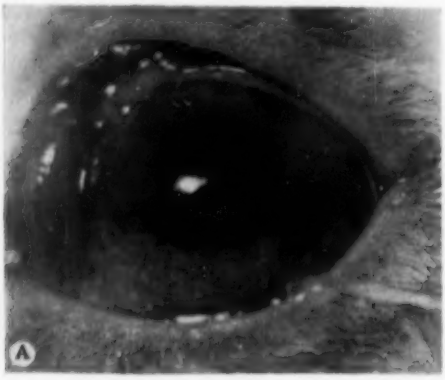
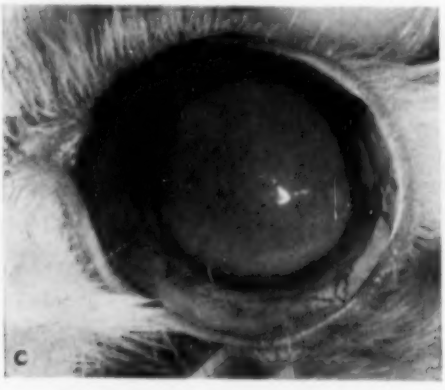
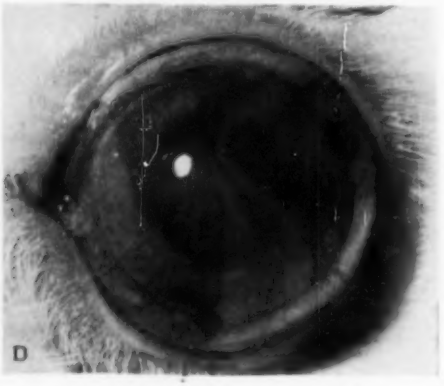


Fig. 3.—*A*, rabbit eye immediately after anterior chamber injection of Efocaine, showing opacity in lower fourth of anterior chamber.

B, rabbit eye one hour after anterior chamber injection of Efocaine, showing opacity of lower two-thirds of cornea.



C, rabbit eye seen days after anterior chamber injection of Efocaine, showing corneal haze and early vascularization.



D, rabbit eye 18 days after anterior chamber injection of Efocaine, showing almost complete vascularization of cornea.

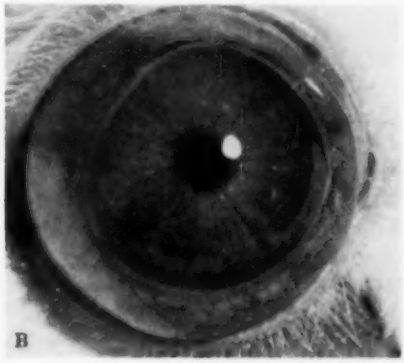
Conclusions: U-0045 caused mild conjunctival reaction when injected subconjunc-

tivally in rabbits. Efocaine caused a severe conjunctival reaction, usually associated with irritative iritis and corneal opacity.

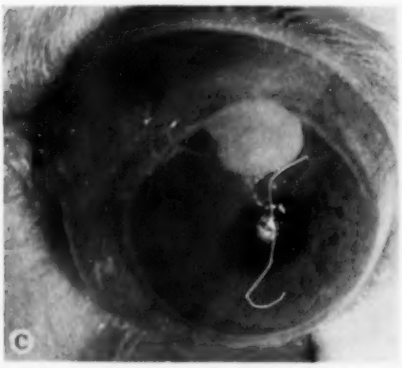
2. Anterior Chamber Injections in Rabbits: (*a*) U-0045 lactate. Injection of 0.1 cc. of 0.2% U-0045 lactate was made into the anterior chambers of 11 rabbit eyes. Faint to moderate diffuse corneal haze associated with some conjunctival chemosis was noticed one and one-half to three hours after the injection of U-0045 in seven eyes, but four remained clear. The conjunctiva of all of the eyes showed mild hyperemia. Most of the eyes returned to normal in from 3 to 10 days. One with severe opacity remained hazy for two months. Two corneas developed an opaque vascularized spot, which persisted for one month. A 0.5% U-0045 solution caused marked irreversible opacity of the cornea, while 0.1% U-0045 produced no reaction.

(*b*) Efocaine. Injection of 0.1 cc. of Efocaine was made into the anterior chambers of six rabbit eyes. Efocaine immediately precipitated upon coming into contact with the aqueous and formed a white flocculent opacity, which filled the lower fourth of the anterior chamber (Fig. 3 *A*). All the eyes immediately became injected and showed chemosis. In one hour the lower one-half to two-thirds of the corneal stroma became hazy, while the uppermost one-half to one-

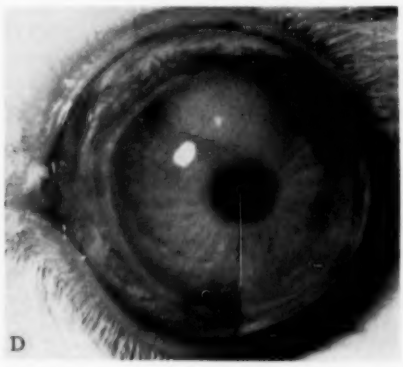
Fig. 4.—*A*, rabbit eye immediately after intracorneal injection of 0.2% U-0045, showing dense opacity.



B, rabbit eye 24 hours after intracorneal injection of U-0045, showing faint residual opacity.



C, rabbit eye immediately after intracorneal injection of Efocaine, showing marked corneal opacity.



D, rabbit eye seven days after intracorneal injection of Efocaine, showing vessels growing into the corneal opacity.

third remained clear (Fig. 3 *B*). The following day the corneas of all eyes showed persistent haze, which was most marked inferiorly, and all had severe chemosis. The corneas showed marked vascularization after about seven days (Fig. 3 *C*). The pupils were semidilated and nonreactive to light, probably due to depression of the iris musculature, as well as the elimination of axon reflexes by the anesthetic.† During the following month the corneas remained opaque and the eyes inflamed (Fig. 3*D*).

Conclusions: A 0.1% U-0045 solution caused no noticeable ocular irritation when injected into the anterior chamber. A 0.2% solution caused mild ocular irritation with transient corneal opacity, however, and 0.5% produced irreversible corneal opacity. Efocaine immediately precipitated in the anterior chamber and remained as an irritant, causing irreversible corneal damage and severe irritation to the eye.

3. Intracorneal Injections in Rabbits: Intracorneal injections were made using 0.1 cc. of 0.2% U-0045 lactate in four eyes and 0.1 cc. Efocaine in five eyes. Control injections of saline and procaine caused little or no reaction.

(*a*) U-0045 lactate. Intracorneal injection of U-0045 lactate 0.2% caused faint corneal opacity with very little ocular reaction (Fig. 4 *A* and *B*). The conjunctiva cleared in from 24 to 48 hours. Corneal opacities cleared in three days in two eyes and four days in two eyes.

(*b*) Efocaine. A precipitation of procaine crystals resulted immediately from the injection of Efocaine, which caused a marked corneal opacity (Fig. 4 *C*). The conjunctiva of all the eyes showed more evidence of inflammation than the eyes injected with U-0045 and required 48 to 72 hours to clear. Two animals developed mild iritis, one of which cleared by the third day and the other on the ninth day. A few vessels grew into the localized corneal opacities of two of the eyes on about the 7th to the 12th day (Fig. 4 *D*). Faint corneal opacity continued for at least two months in the four eyes.

Conclusions: Intracorneal injections of U-0045 caused mild ocular irritation, while Efocaine caused much more marked reaction as well as corneal opacity.

II. OBSERVATIONS ON CLINICAL USEFULNESS OF EFOCAINE AND U-0045

Efocaine and U-0045 seemed to offer promise in controlling postoperative and certain other types of ocular pain. Because of the irritating effects of both Efocaine and U-0045 which had been observed by us to occur when these agents were injected into the anterior chamber, it seemed obvious that their clinical use should be limited to retrobulbar anesthesia. Any ophthalmic surgeon would hesitate to employ a local anesthetic agent for subconjunctival injection or instillation anesthesia for intraocular surgery which produced marked ocular irritation when injected into the anterior chamber. We did, however, repeat in humans work previously done by Bass and Schroeder in animals, on the duration of corneal anesthesia resulting from the instillation of U-0045 into the conjunctival cul-de-sacs.

A. Efocaine.—At the time these studies were done, little was known of the effect of Efocaine. No unfavorable reports had as yet appeared in the literature. Because of the irritation observed in animals, we did employ it with hesitation. It was used for retrobulbar anesthesia in only six eyes, all but two being blind or near-blind, usually with intractable pain. The marked tissue irritation which it uniformly produced, with, in addition in one eye, what was believed to be a destructive lesion to the ciliary and oculomotor nerves, caused us to abandon its further ophthalmologic use.

PATIENT 1.—E. M. was given a retrobulbar injection of 1 cc. of Efocaine because of agonizing prolonged ocular pain due to a severe necrotizing scleritis associated with rheumatoid arthritis. Dramatic relief was obtained, which lasted for one week. Considerable edema of the lids existed prior to the retrobulbar injection, but this definitely increased, and he developed, in addition, definite proptosis as

† Bass and Schroeder.[41] Personal communication to the authors.

a result of the injection. No other ill effects were noted.

PATIENT 2.—H. C. was admitted to the hospital because of an overwhelming endophthalmitis resulting from infection through an Elliot corneoscleral trephine bleb. She was given antibiotics. Because of severe pain, a retrobulbar injection of 1 cc. of Efocaine was made. This relieved her pain for several days, until the infection subsided. Edema of the lids, chemosis, and proptosis seemed to be aggravated by the injection. Corneal anesthesia persisted for seven days, but enucleation had to be performed because of the primary condition.

PATIENT 3.—M. M. received retrobulbar injection of Efocaine for anesthesia during an evisceration operation. Pain was absent after the operation. Healing occurred normally. No undue reaction was experienced, probably because of a pressure dressing which was applied postoperatively.

PATIENT 4.—H. S. was blind in his right eye as a result of occlusion of the central retinal artery and was admitted for a cataract extraction on the other eye. At the time of surgery retrobulbar injection of 1 cc. of Efocaine was made on the side of the blind eye and of the same amount of 10% procaine hydrochloride on the other. Twenty-four hours later the patient had definite ptosis of the right upper lid with moderate edema of the lid and obvious proptosis, which measured 4.5 mm. with a Hertel exophthalmometer. Corneal anesthesia was present. The ptosis lasted for one week, as did the exophthalmos. Corneal anesthesia persisted several days longer.

PATIENT 5.—M. G. had a retrobulbar injection of Efocaine at the time of a retinal detachment operation. She had no postoperative pain but did develop a definite exophthalmos, which, however, was difficult to evaluate because of the retinal detachment operation. This cleared, with no apparent ill effect.

PATIENT 6.—W. K. was admitted to the hospital for strabismus surgery. Retrobulbar anesthesia was obtained by injection of 1 cc. of Efocaine. The following day that eye showed more proptosis and reaction that would have been expected as a result of muscle surgery. She had developed complete ptosis with associated weakness of the superior rectus muscle, accompanied by complete internal ophthalmoplegia and corneal anesthesia. The corneal sensation thereafter remained diminished and the pupillary light reaction sluggish for over four months. The ptosis and paresis of upward gaze required two months to disappear after the retrobulbar injection of Efocaine. It therefore seemed likely that the prolonged anesthesia following the use of Efocaine is similar to that following procaine in oil, i. e., actually a degeneration of the nerves.

Conclusion: Retrobulbar injections of 1 cc. of Efocaine in humans produced nerve blocks lasting a minimum of one week. However, it caused marked inflammatory reactions, as evidenced by proptosis and chemosis. In one case, ptosis, corneal anesthesia, and internal ophthalmoplegia persisted for one month, and nerve function did not entirely return to normal by the end of four months. The severe local reaction and the prolonged nerve blocks following the retrobulbar injection of Efocaine suggested that it probably produced nerve damage. We therefore discourage its further use in ocular surgery except possibly in the treatment of blind, painful eyes. In such cases retrobulbar alcohol injection caused no greater apparent reaction and produced a more permanent effect.

Table II

DURATION OF CORNEAL ANESTHESIA AFTER CONJUNCTIVAL INSTILLATION
(Clinical Study)

PATIENTS	0.2 % U0045		1.0 % PONTOCAINE	
	RECOVERY TIME IN MINUTES		RECOVERY TIME IN MINUTES	
	OBJECTIVE	SUBJECTIVE	OBJECTIVE	SUBJECTIVE
1	65	135	25	30
2	65	165	25	30
3	70	120	25	30
4	60	90	25	30
5	45	80	25	40
6	50	70	30	40
7	40	45	40	45
8	40	45	20	25
9	60	65	60	65
10	40	55	30	30
11	30	75	30	35
12	35	105	20	30
13	45	55	30	45
14	30	30	30	30
15	30	30	30	30
16	45	60	30	45
Average Duration	47	77	30	36

B. U-0045.—1. Conjunctival Instillation of U-0045 Lactate (Table 2): The anesthetic effect of U-0045 lactate, 0.2%, when instilled into the conjunctival cul-de-sacs of human eyes, was compared with that of 1% tetracaine. The following method of instillation was used: A drop of anesthetic solution was first placed into the lower cul-de-sac, followed in 30 seconds by a second instillation over the upper portion of the cornea with the upper lid retracted. Thirty seconds later the eyes were irrigated continuously with saline solution for one minute. Neither anesthetic solution caused corneal damage, although in the majority of the patients U-0045 caused

a severer burning sensation immediately after the instillation. Nearly all the eyes receiving U-0045 showed more persistent conjunctival hyperemia than those receiving tetracaine. The duration of anesthesia was measured in two ways: (1) objectively—the return of the corneal reflex obtained with von Frey hairs—and (2) subjectively—the return of equal sensation in the two eyes according to the patient's observations (using von Frey hairs). The corneal reflex was reestablished on an average of 47 minutes in the eyes receiving U-0045 lactate and in 30 minutes in the eyes receiving tetracaine. Subjective sensation returned to normal in an average of 77 minutes in the eyes receiving U-0045 and in 36 minutes in the eyes that had had tetracaine. These findings agree with those of Bass and Schroeder,[41] who found that, in animals, the anesthetic index of U-0045 was considerably greater than that of cocaine or tetracaine.

We have not carried these observations further because excellent local anesthetic agents are available for surface anesthesia, such as tetracaine, which are not irritating when injected into the anterior chamber.

2. Use of U-0045 Clinically for Retrobulbar Anesthesia: We hoped that, because of the prolonged anesthetic effect of U-0045 observed in animals following retrobulbar injection and the absence of ill effect, it might prove of value clinically in avoiding postoperative pain.

(*a*) A retrobulbar injection of 1.0 cc. of 0.5% U-0045 lactate was given to four patients who required minor surgical procedures. Excellent anesthesia resulted, but the akinesia of the extraocular muscles was disappointing. Careful determination of the duration of anesthesia was possible in view of the relatively trivial surgery which had been done. Extraocular muscle function returned to normal in an average of 8 hours, while the duration of anesthesia varied from 8 to 12 hours.

Table III

RETROBULBAR ANESTHESIA

1½ cc 0.5% U0045	
Cataract extraction	4
Retinal detachment	6
Iridenclesis	1
Iridenclesis & anterior sclerectomy	2
Cyclodialysis	1
Peripheral iridectomy	4
Lysis of anterior synechiae (after corneal transplant)	1
Air injection into ant. chamber	4
TOTAL	23

Table IV

OPERATIONS USING RETROBULBAR INJECTION OF ¾ cc 0.5% U0045 AND ¾ cc 10.0% PROCAINE HYDROCHLORIDE WITH HYALURONIDASE

TYPE OF OPERATION	NO. OF CASES
Cataract extraction	314
Filtering operation for glaucoma	39
Cyclodialysis	18
Iridectomy	20
Keratoplasty	19
Retinal detachments	44
Strabismus	10
Enucleation	8
Other intraocular surgery	68
TOTAL	540

Further observations on retrobulbar anesthesia resulting from the injection of U-0045 lactate were conducted by using 1.5 cc. of 0.5% solution in 19 patients having intraocular surgery (Table 3). Anesthesia was excellent, but its onset required several more minutes than with procaine. This larger group of patients also demonstrated less adequate akinesia of the extraocular muscles than we had been accustomed to obtaining with procaine. The diminished akinesia resulting from U-0045 lactate might possibly be explained by poor diffusion of the anesthetic agent through the tissues.

To overcome this objection, we sought to combine the more rapid onset and more complete akinesia resulting from procaine with the strikingly greater duration of anesthesia from U-0045 by using the two drugs in one solution. Retrobulbar injections containing 0.75 cc. of 0.5% U-0045 and 0.75 cc. of 10% procaine with hyaluronidase were given. For five years one of us (H. S.) has used 1.5 cc. of 10% procaine for retrobulbar anesthesia, no ill effect having been encountered.[42]

This combination has since been used in 520 ocular surgical procedures of various types, no incident which could be attributed to the anesthetic agent being recognized (Table 4). It produces very satisfactory

anesthesia and akinesia for all types of ocular surgery. The incidence and severity of postoperative pain were greatly reduced. When pain does occur with this anesthetic combination, its onset is usually 8 to 12 hours following operation, and it is then usually mild and relieved by 10 grains (0.6 gm.) of acetylsalicylic acid. Postoperative nursing care, as a result, has been greatly simplified. Postoperative vomiting has been virtually eliminated.

3. Control Studies: Control observations were made on a group of 30 patients. Retrobulbar anesthesia was obtained in 10 patients by procaine hydrochloride 10%, in 10 patients by tetracaine hydrochloride 0.1%, and in 10 patients with the above combination of procaine and U-0045, but only the operating room supervisor knew what the individual patient received. The relative absence of pain in patients receiving U-0045 enabled us to identify the patients of this group with relative dependability. Tetracaine was effective for a longer time and permitted less postoperative pain than did procaine.

COMMENT

Clinical and experimental studies were undertaken to compare the duration of anesthesia and the local tissue irritation resulting from the use of two new long-lasting local anesthetic agents, U-0045 and Efocaine, with the same properties of certain local anesthetic agents now used extensively in all fields of surgery. The duration of anesthesia following retrobulbar injection in rabbits was determined, using (1) procaine with and without hyaluronidase, (2) lidocaine with and without hyaluronidase, (3) tetracaine with and without hyaluronidase, (4) U-0045 lactate with and without hyaluronidase, and (5) Efocaine. Procaine hydrochloride produced anesthesia which persisted for an average of 60 minutes; the average duration for lidocaine was 45 minutes, for tetracaine 82 minutes, for U-0045 312 minutes, and for Efocaine 2 weeks and longer.

The ability of the different anesthetic solutions to diffuse through orbital tissues seemed to vary, as indicated by the incidence of successful blocking of the ciliary nerves following the retrobulbar injection of a given amount of solution. Procaine, tetracaine, and lidocaine produced almost uniformly good retrobulbar anesthesia in rabbits, after each injection. U-0045 lactate apparently diffused through the orbital tissues somewhat less well, because anesthesia resulted in only 10 of 18 injections. Efocaine, which is known to precipitate immediately upon contact with tissue fluids, blocked the ciliary nerves in only 6 of 19 injections. When hyaluronidase was added to anesthetic solutions, the number of successful blocks increased, but the duration of anesthesia was slightly reduced, probably due to increased diffusion with more rapid elimination from the tissues.

Efocaine and U-0045 both caused local tissue irritation, Efocaine the severer. Procaine, tetracaine, lidocaine, and U-0045 produced no apparent reaction after retrobulbar injection. Efocaine, however, caused marked irritation, as indicated by edema of the lids and conjunctiva accompanied by considerable proptosis. Procaine, tetracaine, and lidocaine caused no reaction when injected subconjunctively or intracorneally in rabbits. Mild conjunctival hyperemia resulted from the subconjunctival injection of U-0045. Corneal haze could be produced by placing it intracorneally or into the anterior chamber. This reaction was severe after the injection of 0.5% solution, mild and transient after 0.2% solution, and absent with the 0.1% solution. The reactions were transient, and the cornea cleared in a few days in nearly all instances with the weaker solution. Efocaine caused a much severer reaction, associated with signs of iritis and corneal opacity. When injected subconjunctivally, intracorneally, or into the anterior chamber, Efocaine could be seen to precipitate immediately in the tissues. When injected into the anterior chamber, the precipitate filled the lower portion of the chamber, where it persisted and caused marked permanent complete corneal opacification and heavy vascularization, with degeneration of the eye.

Clinical observations with retrobulbar injections of Efocaine resulted in our discon-

tinuing its use. Marked edema of the lids, chemosis, and proptosis resulted. The resulting duration of anesthesia continued for such a long period that we suspected one of the constituents of Efocaine of causing nerve damage, similar to the action of procaine in oil. One patient developed proptosis, which persisted for two months, and complete internal ophthalmoplegia with corneal anesthesia, from which she had not completely recovered by four months.

The durations of corneal anesthesia following the conjunctival instillation of U-0045 lactate 0.2% and tetracaine 1.0% were compared clinically. The corneal reflex was abolished for an average of 47 minutes after instillation of U-0045 lactate and for 30 minutes after tetracaine. Subjectively, normal sensation returned in an average time of 77 minutes after U-0045 and 36 minutes after tetracaine instillation. This was considered further evidence of the prolonged anesthetic effect of U-0045. U-0045 lactate caused more conjunctival hyperemia than tetracaine, but neither caused corneal damage. We did not use instillation of U-0045 for intraocular surgery because of the irritation that it could produce when injected into the anterior chamber of animals and because so many excellent anesthetic agents were available for the purpose. We did use it clinically for retrobulbar anesthesia to utilize its prolonged anesthetic effect to prevent postoperative pain.

In an initial, small group of patients (Table 3), 1.5 cc. of 0.5% U-0045 lactate injected into the muscle cone gave excellent anesthesia, which persisted for six to eight hours and longer, as determined by postoperative discomfort. Most of the patients had little or no postoperative pain.

Although U-0045 lactate gave excellent anesthesia, it did not seem to produce as complete akinesia of the extraocular muscles as did procaine. Because our observations in rabbits seemed to show that it did not diffuse through tissues as well as procaine, we sought to obtain the effect of both by combining 0.75 cc. of 0.5% U-0045 lactate with 0.75 cc. of 10% procaine containing hyaluronidase. This combination seemed excellent, and now has been used on more than 540 eyes over a period of 18 months (Table 4) in all types of intraocular and extraocular muscle surgery. Postoperative pain is often eliminated. When it does occur, it is not until 8 to 12 hours after operation, and is then usually slight. Postoperative restlessness, nausea, and vomiting are likewise tremendously reduced. Nursing care has been greatly simplified. We did not encounter any ill effect which could be attributed to the anesthetic agent, even though it does have definite irritative properties in solutions of 0.2% or more.

Local tissue irritation following the injection of U-0045 was observed by us in rabbits and clinically by Dripps.§ He employed it for regional nerve blocks (intercostal, brachial, cervical, stellate, paravertebral, and sympathetic) and noted necrosis at the site of the skin wheal in eight patients, all of whom received 0.2% or stronger solutions. It occurred in 3 of 34 patients (10%) in whom 0.5% U-0045 was used, in 5 of 116 patients (4.3%) in whom 0.2% U-0045 was used, and in none when a concentration of less than 0.2% was injected. In addition, two patients whose brachial plexus was blocked with 25 cc. of 0.5% U-0045 developed a brachial plexus neuralgia which persisted for several months. We have noted no similar instance of neuralgia following intraocular surgery, but this might be explained by our use of 0.25% solutions, a concentration which gives only mild irritation when injected into the anterior chamber of a rabbit eye.

Although, at least partially, because of its irritative qualities, U-0045 is not the final answer to the problem of long-lasting local anesthesia, in our opinion it represents a forward step in this direction and is of considerable value in ocular surgery when employed in retrobulbar injections. We are now using it for all of our ocular surgery requiring retrobulbar anesthesia at the Hospital of the University of Pennsylvania, and we believe

§ Dripps, Robert D.: Personal communication to the authors.

that it deserves more extensive trial by other ophthalmic surgeons. We do not recommend its use for subcutaneous or subconjunctival injections or for instillation anesthesia, because of its irritative qualities when injected into the anterior chamber of the eyes of rabbits. Its use is also contraindicated for spinal anesthesia for the same reason. However, in our experience with over 540 operations it has been safe for retrobulbar injection when diluted to 0.25% by combining it with procaine solution. The anesthesia which results is excellent and of sufficiently long duration to prevent much postoperative pain.

SUMMARY

Observations are reported on the duration of anesthesia following the retrobulbar injection of procaine, lidocaine (Xylocaine), tetracaine (Pontocaine), U-0045, and Efocaine. Procaine and lidocaine were effective for somewhat less and tetracaine somewhat longer than one hour. U-0045 and Efocaine had a much longer effect.

Efocaine produced such marked tissue reaction that its use is contraindicated in ocular surgery.

U-0045, which has an anesthetic effect of 8 to 12 hours, offers promise of future usefulness in operations upon the eye. It produces excellent anesthesia, which is of sufficient duration to avoid most postoperative pain.

U-0045 is somewhat irritating to tissues. Although 0.5% solution injected into the anterior chamber causes permanent corneal opacity, 0.2% solution produces only transient corneal haze, and 0.1% solution gives no signs of ocular irritation. A injection of 0.75 cc. of 0.25% solution for retrobulbar anesthesia in over 540 patients produced no clinical signs of untoward effect.

Tetracaine, although not as effective as U-0045, causes no tissue irritation and has a considerably longer effect clinically than procaine or lidocaine. Although tetracaine is too toxic to be injected in large amounts, the small quantity needed for retrobulbar anesthesia is well within safe limits and give excellent anesthesia of significantly greater duration than procaine or lidocaine.

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TONOGRAPHIC MEASUREMENTS IN ENUCLEATED EYES

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IT WAS THE purpose in this investigation to examine the relationship of intraocular pressure, volume of the eye, and rate of outflow of the aqueous humor by direct methods and to evaluate these factors as they bear on the indirect methods of clinical tonography.

The present work constitutes the second part of a general study of the outflow of the aqueous humor, the first part of which was the development and application of tonography.* A third part, to be reported separately, is concerned with the anatomical and physiological factors responsible for the resistance to outflow from normal eyes and glaucomatous eyes.[4]

Clinical tonography has indicated that the outflow of aqueous normally encounters a resistance which becomes greater than normal in all types of glaucoma, and that this increased resistance is the principal cause of increased intraocular pressure in glaucoma.[3] Also, in conjunction with gonioscopy, tonography has helped establish a satisfactory mechanical explanation for increased resistance in the type of glaucoma in which the iris presses against the filtration meshwork in the angle ("narrow-angle," or "angle-closure" glaucoma) and in glaucoma due to peripheral anterior synechia. In glaucoma in which the angle appears normal gonioscopically ("wide-angle," or "open-angle" glaucoma) tonography has provided evidence that an obstruction to outflow is, nevertheless, the cause of the glaucoma. Clinical tonographic measurements have been utilized in studying the effects of surgery and drugs in treatment of glaucoma, as well as for investigating the basis for spontaneous variations of intraocular pressure. In general, good agreement in results of tonography has been obtained by various investigators, but in all instances the interpretation of results has necessarily been subject to limitations imposed, on the one hand, by the same sort of instrumental limitations as those encountered in regular tonometry, and, on the other hand, by certain assumptions regarding the relationship of the measured rate of change of pressure and volume in the living eye to the rate of formation and outflow of the aqueous humor. Further assumptions have been made regarding the ocular blood circulation and the influence of the back-pressure in the veins which receive the outflow of aqueous. These limitations and assumptions have been discussed at length elsewhere.†

If some of these uncertainties involved in tonography could be reduced, the significance of tonographic measurements would, of course, be enhanced. The present investigation attempts a step in this direction. In particular, it has seemed worth while to examine the validity of Friedenwald's estimate for the coefficient of scleral rigidity and to compare the facility of aqueous outflow in enucleated eyes with that in life. The calibra-

Purchase of part of the apparatus was financed by the Snyder Ophthalmic Foundation.

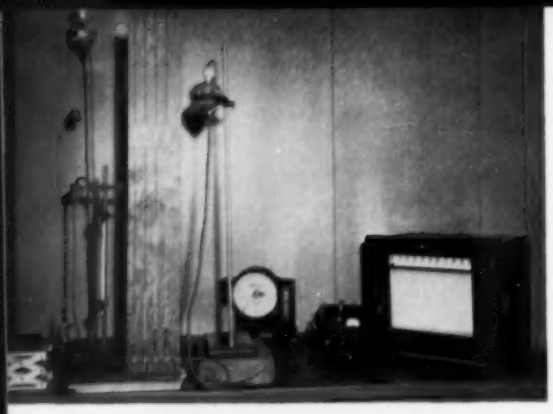
Normal enucleated eyes were supplied for this study by the Boston Eye Bank.

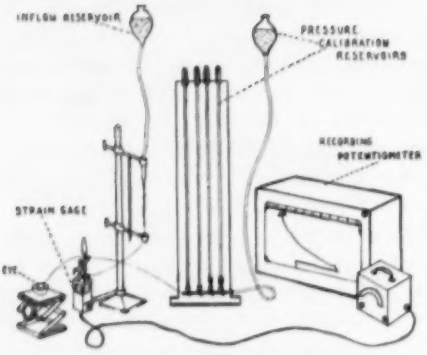
From the Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

This investigation was supported by Research Grant B-218 of the Institute of Neurological Diseases and Blindness of the National Institutes of Health, U. S. Public Health Service.

* References 1, 2, and 3.

† References 2, 3, and 5.





Figs. 1 and 2.—Picture and diagram of the apparatus which has been employed for measuring intraocular pressure and for determining scleral rigidity and facility of outflow in enucleated human eyes and in living and enucleated rabbit eyes.

tion of the type of electronic tonometer which is employed in tonography has also been examined.

The reason for wishing to ascertain whether Friedenwald's estimate of scleral rigidity is correct is that proper evaluation of the rigidity of the coats of the eye has an important influence on the accuracy of calibration of clinical tonometers, as well as on measurements of aqueous outflow by tonography. The relationship between the change in pressure and the change in volume of an eye is indicated by a proportionality constant, known as the "coefficient of scleral rigidity." Friedenwald has arrived at a numerical value of 0.0215 for average normal human eyes.‡ This value was derived principally from measurements of the relative stretchability of the sclera of the living eye as determined by the Schiøtz tonometer.

‡ Reference 7, pp. 138-141.

It is on this value that tonometric and tonographic measurements are now based. In view of the significance of this value in clinical investigation, it seemed worth while to make a comparison with values measured by more direct means in enucleated eyes and to inquire into the basis for any differences which might be found.

The comparison of facility of outflow in life and after death or enucleation might be expected to yield some information regarding the true nature of the resistance to outflow which is measured by tonography. (It will be recalled that the coefficient of facility of aqueous outflow has been regarded as a measure of the ease with which the aqueous humor can escape from the eye. In clinical tonography this facility of outflow is determined in units of cubic millimeters [or microliters] of outflow per minute per millimeter Hg of intraocular pressure).

METHODS

For these experimental studies special methods and instrumental techniques have been developed. The investigations have been carried out principally on human enucleated eyes, and also on living and enucleated rabbit eyes. A rather detailed description of these methods seems warranted, because these methods have proved to have considerable usefulness, not only in the present studies but also in further studies on the nature of the outflow channels of normal and glaucomatous eyes, to be reported subsequently.

The intraocular pressure has been recorded continuously during determination of scleral rigidity and facility of outflow by means of an electronic strain gauge, which was connected to the eye through a fine, flexible cannula. (The strain gauge is a commercially available device which translates pressure into electrical resistance to provide for automatic electric recording on a moving paper strip.‡‡ The strain gauge has a great advantage in sensitivity over a conventional water manometer, since with varying pres-

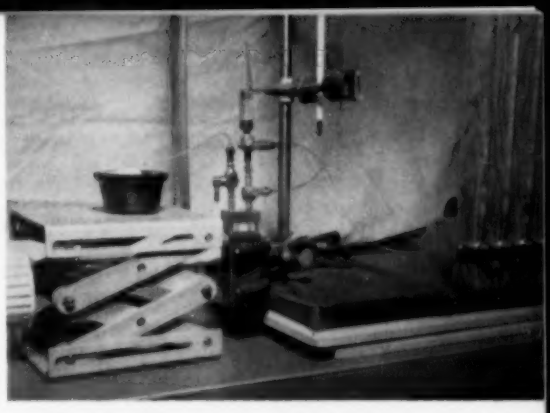
‡‡ Model P23B, manufactured by Statham Laboratories, Los Angeles 64.

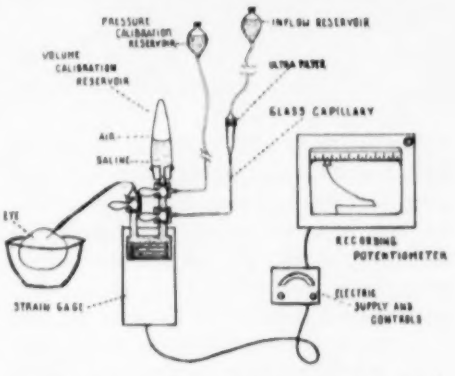
sure the strain gauge involves relatively little change in volume within the instrument.) For calibration of the strain gauge, a connection was provided through appropriate stopcocks to a set of standard water manometers with pressure levels graded from 0 to 50 mm. Hg equivalent. This, and all apparatus to be described subsequently, are shown in Figures 1 through 4.

Connection between eye and strain gauge was made with polyethylene tubing (0.034 in. inside diameter). One end of the tubing was equipped with the shaft of a #27-gauge needle (⅜ in. long) for insertion into the eye.§ (This size of tubing and needle was determined to be large enough and the recording equipment fast enough so that no significant error would be introduced by excessive damping in the applications to be described.) Enucleated eyes with cornea uppermost were supported in isotonic saline up to the level of the rectus muscle insertions, and the eye was kept from moving about by a loose, submerged nest of absorbent cotton fibers. The #27 needle-cannula was inserted into the anterior or the posterior chamber through the cornea or the sclera, as the experiment demanded. Insertion of the needle was accomplished by means of a surgical needle holder, while an adjacent rectus tendon was grasped with fixation forceps. The insertion was made in a direction away from the tendon so that only a small portion of the globe would be subjected to tension during the manipulation.

For injection of known volumes of solution into the eye for measurement of scleral rigidity, the strain gauge was equipped with an auxiliary glass chamber having an approximate 1.3 cc. of air space. This chamber is labeled in the illustrations as the "volume calibration reservoir." It was connected to the strain gauge through a three-way stopcock, which also served for connection with the reference or pressure-calibrating manometer.

§ The needle was adapted to the inside diameter of the tubing by removing the standard hub and substituting for it a tiny drop of solder.





Figs. 3 and 4.—Picture and diagram of the strain gauge and its stopcocks, with connections to the eye and to various devices for volume calibration, pressure calibration, flowmetering, and electric recording.

For continuous inflow into the eye at a known rate, the strain gauge was also equipped with a capillary flowmeter and reservoir system, connected through a separate stopcock. An ultrafine fritted glass filter was interposed between the reservoir and the fine glass capillary of the flowmeter device to prevent obstruction of the capillary by foreign particles and micro-organisms.

The recording system which was employed for the strain gauge consisted of either the Sanborn amplifier and recording galvanometer, which is employed in clinical tonography, or, for greater sensitivity, a wide-chart recording potentiometer, such as shown in the illustrations. Most measurements were made with the wide-chart recorder. This instrument had a full-scale sensitivity adjustable from 5 to 50 mv. and full-scale pen travel of ⅔ second. The chart travel was 0.75 in. per minute. The potential applied to the Wheatstone bridge, of which the strain

gauge formed a part, was obtained from a battery source of 4 volts.

The various procedures for which this apparatus proved to be well suited were (1) continuous recording of intraocular pressure, (2) determination of the scleral rigidity, (3) determination of the facility of outflow from the spontaneous rate of decline in the pressure in the absence of inflow, (4) determination of the facility of outflow under steady-state conditions, and (5) calibration of tonometers. Methods for carrying out certain of these measurements will now be described.

Determination of Coefficient of Scleral Rigidity.—This was accomplished by measuring the amount of change in pressure which was induced in an eye by the injection of a known volume of fluid (0.9% sodium chloride). Connection to the eye for this measurement and injection was made with the fine #27-gauge needle-cannula through the cornea near the limbus or through the limbal sclera into the posterior chamber. With the stopcocks set so that only the eye was connected to the strain gauge, the intraocular pressure was recorded. (In enucleated eyes or in eyes of dead animals the pressure was found to be gradually falling, depending upon the initial pressure level and the facility of outflow. In living eyes in anesthetized rabbits the pressure usually remained fairly constant). Now, without affecting the eye and strain gauge, the three-way stopcock of the volume calibration reservoir was positioned so that this reservoir was connected directly to the pressure calibration reservoir in order for the air in the volume calibration reservoir to be compressed with a known pressure, usually 50 mm. Hg. Next, the three-way stopcock was rotated so that the volume calibration reservoir was disconnected from the pressure calibration system and was connected instead with the eye-strain gauge system to deliver saline solution to the eye. Typically, the flow from volume calibration reservoir to eye was at first rapid, until the pressures were essentially equilibrated, and then slower, dependent upon the outflow from the eye. A typical recording from the strain gauge during this procedure is diagrammed in Figure 5. At *A* the recording was from the eye alone; at *B* the injection of fluid from the volume calibration reservoir began, and there was a momentary overshoot of the pressure in the gauge above that in the eye; at *C* the pressures in the system were essentially equilibrated but gradually falling, owing to outflow from the eye. (Equilibration of pressures along *C* is demonstrable by shutting off the stopcock either to the eye or to the volume reservoir at this point and finding the pressure of each equal to *C*). For purposes of calculation, it would be desirable to know the pressure at which equilibration would have occurred if it were essentially instantaneous and uninfluenced by outflow from the eye. This pressure (*E*) may be approximated by the point of intersection of line *C* extrapolated to line *AB*. Then the volume delivered into the eye-gauge system from the volume reservoir is readily determined from *E* and the original pre-set pressure in the volume reservoir, for the volume reservoir has been calibrated so that the relationship between pressure and volume in

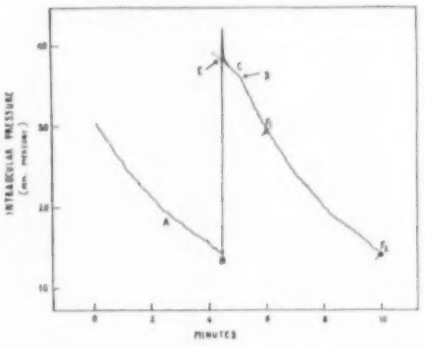


Fig. 5.—Copy of a recording from an enucleated normal human eye showing along curve *A* and along curve F_1—F_2 the spontaneous decline in pressure which results from the outflow of intraocular fluid. The pressure was raised at *B* by an injection from the volume calibration reservoir. From this recording both the coefficient of scleral rigidity and the coefficient of facility of outflow may be determined by methods described in the text.

it is accurately known.‖ Next, to determine from the volume delivered to the eye-gauge system the proportion delivered to the eye itself, only a small deduction is needed (0.1 cu. mm. per millimeter Hg) for the volume change which took place within the strain gauge in going from B to E. Now knowing the volume (ΔV) which was introduced into the eye, and which resulted in the rise in intraocular pressure from B to E, it is easy to calculate the scleral rigidity from Friedenwald's equation, where the coefficient of scleral rigidity equals $\frac{\log \frac{P_1}{P_2}}{\Delta V}$, or $\frac{\log \frac{E}{B}}{\Delta V}$.

Facility of Aqueous Outflow from Eye.— This was determinable by two methods; in the first method it was determined from the rate of spontaneous decline in pressure in the absence of an inflow. For determination by this method there was required only a continuation of the procedure which was employed for measurement of scleral rigidity. As shown in Figure 5, when the pressure was seen to be falling smoothly along line C (with the pressure very nearly equilibrated between the volume calibration reservoir and the eye-gauge system), the stopcock was turned (at D) so that inflow from the volume reservoir was discontinued and only the strain gauge was connected to the eye. The pressure then was found to fall more rapidly along line F. For calculation of the facility of outflow, a convenient portion of line F, usually several minutes long, was selected, and the volume which flowed out of the eye during this interval was calculated from the measured change in pressure and the coefficient of scleral rigidity, which was already determined in steps A through E. A small change in volume within the gauge has also been taken into account. The volume which flowed out of the eye in going from pressure P_1 to P_2 was calculated from the formula:

$$\Delta V = \frac{\log \frac{P_1}{P_2}}{\text{scl. rigidity}} + 0.1\ (P_1 - P_2).$$

The coefficient of facility of outflow was obtained from calculations based on the known proportionality of rate of outflow $\frac{\Delta V}{T}$ to intraocular pressure. In the present instance, as in clinical tonography, the intraocular pressure was changing during measurement, and the arithmetical average of the pressure (Ave.P) going from P_1 to P_2 has been employed in the following equation:

$$\text{Coefficient of facility of outflow} = \frac{\Delta V}{(T)\ (\text{Ave.}P)}.$$

Thus, the recorded data, such as that exemplified in Figure 5, serve for the calculation of the coefficient of facility of outflow, as well as the coefficient of scleral rigidity.¶

A second method for determination of the facility of outflow was based on measurement at constant pressure, where no change in ocular volume, and therefore no consideration of scleral rigidity and no change in gauge volume, was involved. For this method the stopcocks were positioned so that the strain gauge and eye were connected only to the glass capillary and inflow reservoir (shown in Figs. 1 through 4). The inflow system was precalibrated (by accurate weighing of effluent), so that the relationship between the rate of flow and the pressure differential across the capillary were well established. With this system in operation, the pressure differential across the capillary was determined by the height of the inflow reservoir

‖ The amount of solution which is delivered with graded pressure changes in the volume calibration reservoir was determined independently by weighing the effluent to the nearest 0.1 mg. on a torsion balance. Typical delivery was 2.00 cu. mm. per millimeter Hg change in pressure for the range 0 to 50 mm.

¶ The calculations corresponding to the recorded data of Figure 5 (normal enucleated human eye No. 7-14-54-B) are as follows:

ΔV of eye from B to E =
$2.00\ (50 - 38.2) - 0.1\ (38.2 - 14.7) = 21.5$ cu.mm.

$$\text{Coefficient of scleral rigidity} = \frac{\log \frac{38.2}{14.7}}{21.5} = 0.0193$$

$$\Delta V \text{ of eye from } P_1 \text{ to } P_2 = \frac{\log \frac{29.7}{14.7}}{0.0193} = 15.7 \text{ cu.mm.}$$

Time from P_1 to P_2 = 4 minutes;
Ave.P = 21.4 mm. Hg.

$$\text{Coeff. of facility of outflow} = \frac{15.7 + 0.1(29.7 - 14.7)}{4\ (21.4)}$$
$= 0.20$ cu.mm./min./mm. press.

and by the intraocular pressure. Since the intraocular pressure was continuously recorded, both pressures were known at all times.#

Given sufficient time, the whole system was found to achieve a steady state, with the intraocular pressure constant and outflow equal to inflow. The same steady state was approached irrespective of whether the inflow initially was greater than the outflow (intraocular pressure rising) or vice versa. The coefficient of facility of outflow (C) was calculated from the steady-state intraocular pressure (P) and the rate of flow (K): $C=\frac{K}{P}$.

Calibration of Reference Standard Tonometers on Enucleated Eyes.—This may be accomplished by means of the strain gauge and the associated apparatus, which has already been described. The tonometer is applied to the eye while the intraocular pressure is recorded continuously. Then both P_o ("closed manometer" pressure) and P_i ("open manometer" pressure) may be read from the paper strip, with only a small correction of P_o for change in volume within the strain gauge. To compensate for the influence of any abnormality of scleral rigidity on the value for P_o, the coefficient of scleral rigidity is measured, as described in a foregoing section, so that the experimental P_o may be corrected to correspond to standard scleral rigidity. Details of the calculations have been published elswhere.[7]

RESULTS

A test of the validity of the present method for determination of facility of outflow and scleral rigidity was made by comparing the values obtained by the two separate methods which have been described for facility of outflow. It may be recalled that one method, which will be referred to as the "kinetic" method, involved determination of the scleral rigidity, and that the other method, to be referred to as the "steady-state" method, was quite independent of scleral rigidity. Measurements by the two methods were compared in 18 enucleated human eyes. The results were in satisfactory agreement, giving an average value for the coefficient of facility of outflow (at room temperature) of 0.177 cu. mm. per minute per millimeter Hg by the "kinetic" method and 0.178 cu. mm. by the "steady-state" method. For individual eyes the average disparity between the two methods was 0.027 cu. mm. These results signify excellent consistency in the methods for determining scleral rigidity and facility of outflow, despite moderate experimental error in individual measurements.

Evidence has been obtained from other observations that determination of scleral rigidity by the present method is independent of variation in facility of outflow. Thus, it was found that in pairs of eyes enucleated from individual rabbits the values for scleral rigidities remained the same even when a large difference in facility of outflow was caused by an artificial leak in one of the eyes.

Coefficient of Scleral Rigidity.—This was measured in 29 normal human adult eyes within 24 hours after enucleation and was found to average 0.0163. Maximum and minimum values were 0.0215 and 0.0110. These eyes were, with one exception, removed after death and were measured either directly or after storage in a refrigerated sterile chamber containing isotonic saline solution. Measurement could seldom be started earlier than 3 hours after death; however, the one eye which was removed from a living patient (enucleated because of a melanoma in the fundus) was studied 15 minutes after enucleation. The coefficient of scleral rigidity for this eye was 0.0194, somewhat above the average for the whole group. Among the eyes removed after death, no correlation was found between the degree of scleral rigidity and the time after enucleation, ranging from 3 to 24 hours. No disturbances of scleral rigidity by the measurement pro-

This capillary flowmeter operated on a principle different from, and more convenient than, that of another type of flowmeter, in which the rate of movement of an air bubble must be timed. In the present flowmeter the rate of flow was directly proportional to the difference in pressure from end to end of the capillary.

cedure itself was detected, for no significant alteration of the scleral rigidity was found during repeated measurements on individual eyes in the pressure range of 10 to 45 mm. Hg. (It has been reported that raising the intraocular pressure may stretch the sclera and increase its rigidity, but this phenomenon is probably observed only at higher pressures, e. g., 75 mm. Hg.)

The difference between Friedenwald's average clinical value of 0.0215 and the average value for enucleated eyes of 0.0163 could be related to some rapid change in the coats of the eye at death. To test this hypothesis, it would be valuable to have measurements by a single method before and after interruption of the ocular circulation, but in human patients this is difficult to accomplish. In rabbits, however, measurements were obtainable by the direct cannulation method, first, with the rabbit asleep under the influence of pentobarbital, and then after death from an overdose. Repeated determinations during life and for several hours postmortem revealed no change in scleral rigidity at the time of death, but a gradual decrease in rigidity during the first hour or two post mortem to a relatively constant state of abnormal flaccidity. This course is illustrated in the Table. These results differ from those of Wessely, who reported abnormal flaccidity in the first few hours after death, and then excessive rigidity.[6]

The decrease in scleral rigidity which we have found to take place in rabbits soon after death provides a reasonable explanation for the difference between the values determined in this study for the rigidity of enucleated human eyes and the estimate obtained by Friedenwald for living eyes. These observations support the validity of Friedenwald's estimate, as well as his criticism of earlier tonometer calibrations, which were made on enucleated eyes without sufficient regard for abnormality of scleral rigidity.

Coefficient of Scleral Rigidity

Rabbit A		Rabbit B	
Status	Coefficient Rigidity	Status	Coefficient Rigidity
Living	0.0215		
	0.0188		
	0.0201		
Ave.	0.0201		
Dead; eye in situ:		Dead; eye in situ:	
Time post mortem		Time post mortem	
6 min.	0.0239	6 min.	0.0235
16 min.	0.0185	42 min.	0.0194
27 min.	0.0210	100 min.	0.0179
29 min.	0.0218	135 min.	0.0134
67 min.	0.0174	170 min.	0.0122
72 min.	0.0158		
76 min.	0.0169		
Contralateral eye Enucleated Refrigerated 16 hr.	0.0167		

The factors responsible for decrease in scleral rigidity after death are obscure. The decrease is not immediately related to interruption of circulation, since the onset is slow, like that of rigor mortis. The behavior in the flaccid state may be altered by artificial physical distortion, such as by abnormal stretching; but in experiments in which the influence of moderate sustained variations of temperature, pH, or concentration of sodium chloride was examined no significant effect from these factors was detected. Only when the pH was raised above 10.5 or lowered below 3.5 were marked effects produced. Exposure to alkali or acid beyond these limits caused a contraction of the globe. It is of some incidental interest that the onset of contraction from exposure to pH 11.5 or

pH 2.9 was significantly retarded in the presence of the corneal epithelium, presumably owing to slow penetration, but that at more extreme values of pH the contraction was prompt irrespective of the presence of the epithelium.

Coefficient of Facility of Aqueous Outflow.—This factor was measured in enucleated human eyes by the two procedures which were described in the section on "Methods," and the results were the same with the two methods. The average value for coefficient of facility of outflow of 31 enucleated human eyes at room temperature was 0.208, which corresponds to 0.27 at 37 C. body temperature when correction is made for the influence of temperature on the viscosity of water.* This is to be compared with an average value of 0.233 obtained by tonography on 171 normal eyes in patients.[4]

It appears from these two sets of measurements that the coefficient of facility of outflow given by tonography in life is not much different from the facility of outflow after enucleation. A comparison would be better made on the basis of measurements on the same eyes before and after enucleation, but only in one instance has this been accomplished. In this one eye, which was enucleated because of a melanoma in the fundus, the facility of outflow was found to be 0.30 by tonography before enucleation and 0.29 (corrected to 37 C.) by cannulation and measurement 15 minutes after enucleation.

Considerable significance may be attached to the finding that the facility of outflow in life is close to, or possibly the same as, the facility of outflow in enucleated eyes. If the observed similarity is not coincidental, and this seems highly unlikely, this finding indicates that most of the normal resistance to outflow may be attributed to a rather stable structure (or stricture) within the eye, rather than to some function of the external vascular or nervous system. This may be considered to constitute a step toward eventual determination of the nature of the increased resistance in glaucoma. It has, therefore, seemed quite worth while to pursue the examination of various factors which influence the facility of outflow both in life and after enucleation, and this has been undertaken in an experimental study, to be reported separately.[4]

CALIBRATION OF TONOMETERS

As part of the effort to establish the accuracy of tonographic determinations of facility of outflow in patients, a calibration of the electronic tonometers employed in tonography was carried out on enucleated human eyes, employing the methods described earlier in this report. The experimental results were corrected for the abnormality in scleral rigidity in enucleated eyes as compared with the rigidity in life (as estimated by Friedenwald), and also for abnormality of the plungers in individual test tonometers. Abnormalities in the plungers were evaluated by comparisons on patients' eyes and by photomicrographic measurements.† The details are probably not of sufficient general interest to warrant reporting here, but these data have led to the conclusion that recently published calibration data for the mechanical Schiøtz tonometer[7] are also appropriate for the type of electronic tonometer employed in clinical tonography.

COMMENT AND CONCLUSIONS

The methods which we have described for determining scleral rigidity and facility of

* Variation of temperature was found to influence the rate of outflow approximately in proportion to the change in viscosity of water.

The values for coefficient of facility of outflow in the individual enucleated eyes (adjusted to correspond to 37 C.) were as follows: 0.244, 0.169, 0.182, 0.234, 0.247, 0.468, 0.286, 0.442, 0.454, 0.376, 0.254, 0.182, 0.390, 0.234, 0.191, 0.143, 0.234, 0.130, 0.100, 0.442, 0.610, 0.302, 0.273, 0.239, 0.221, 0.311, 0.156, 0.208, 0.182, 0.247, and 0.202.

† Members of the Committee on Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology, made a comparison of measurements on normal patients' eyes, employing electronic tonometers having plungers of varying sharpness. Photomicrographic measurements and comparison of the sharpness of these plungers were made by Dr. Friedenwald, and the most desirable contour was ascertained.

outflow in enucleated eyes we believe to be valid because excellent consistency was found when results from two independent methods were compared. Thus, values for facility of outflow which were determined by a simple steady-state, constant-flow method agreed well with values obtained from the same eyes by a method which involved evaluation of the scleral rigidity. The most obvious source of error in the procedures which we have described would be leakage about the cannula. However, we have found that even tiny leaks are recognizable with the aid of a low-power binocular biomicroscope, and we have discarded all measurements in which leaks were detected. In any instance in which a leak may have gone undetected, the value for facility of outflow would be erroneously high, but no error would be introduced into the determination of scleral rigidity.

The tonographic method for measurement of facility of outflow is still subject to a number of uncertainties, but with our independent evaluations of scleral rigidity and tonometer calibration we feel more secure in the validity of the data which are employed in this method for determination of pressures, volume change, and facility of outflow.

Comparison of the facility of outflow in enucleated eyes and in the eyes of patients has, unfortunately, involved the employment of different methods of determination (cannulation and clinical tonography) in the two cases. Since in both cases similar values for facility of outflow have been found, it might be concluded that the determination of facility of outflow by tonography agrees fairly well with the determination by direct cannulation, and that only a small change in the facility of outflow is produced by enucleation. On the other hand, these same results might also be explained by coincidental mutually compensatory differences in the methods and in the eyes. We have no reason to consider this second possibility very seriously, and what comparisons of facility of outflow we have made by cannulation in the eyes of rabbits have indicated little difference in life and after death.‡

If the simplest interpretation of our results is correct, then most of the normal resistance to outflow which is present during life persists after enucleation and is therefore subject to examination uncomplicated by influences from the general circulatory and nervous systems. With these observations to serve as normal controls, an analogous comparison of resistance to outflow in glaucomatous eyes clinically and after enucleation becomes the logical next step.

SUMMARY

Methods have been developed for measurement of pressure in enucleated eyes (and in eyes of living animals) and for determination of scleral rigidity and facility of aqueous outflow in these eyes.

In enucleated normal human eyes the scleral rigidity some hours after death is less than has been estimated by Friedenwald for normal eyes in patients. However, explanation for this difference and support for Friedenwald's estimate are provided by measurements on rabbits which show the scleral rigidity to decrease spontaneously during the first hour or two after death.

Calibration of the electronic Schiøtz tonometer on enucleated normal human eyes, with correction for abnormality of scleral rigidity and for variation of plunger sharpness, gives results in satisfactory agreement with the most recent calibration data for the mechanical Schiøtz tonometer.[7]

The average normal facility of outflow from enucleated human eyes determined by cannulation is only a little greater than the average normal facility of outflow found clinically by tonography (0.27, as compared with 0.233). The principal significance which has been attached to this comparison is that most of the resistance to outflow normally present in vivo appears to persist after enucleation. This suggests that a stable structure, rather

‡ It remains to be established whether cannulation of the eye in life is itself without influence on the facility of outflow.

than some function of the general circulatory system or nervous system, is responsible for the resistance. This finding is thought to constitute a step toward evaluation of the factors responsible for resistance to outflow in normal and in glaucomatous eyes.

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MORPHOLOGY OF THE SENSORY NERVE APPARATUS IN STRIATED MUSCLE OF THE HUMAN EYE

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PREVIOUS neurohistological investigations of the nervous system of the striated muscles of the human eye are primarily concerned with the motor and vegetative nerves and largely neglect the sensory apparatus (Boecke,* Kirsche,[9] Wolter †). Since a systematic study of the latter is not available, a detailed description of the sensory nerves and endings will be given in this contribution.

MATERIALS AND METHODS

Normal striated muscles of the human eye were used exclusively. We applied a modification of the Gros-Schultze silver technique (Wolter [17]) and the silver carbonate method without reduction (del Rio Hortega), the latter proving of particular value (Scharenberg and Zeman [13]). Both methods permit exact microphotographic recording. Reconstructions by drawing are used to describe particularly complicated structures.

HISTOLOGICAL DESCRIPTION

Six distinctly different sensory end-organs can be distinguished in the striated muscles of the human eye.

Type 1. Sensory muscle spindles (Figs. 1 and 2) built of thick myelinated nerves which coil in an irregular manner around the muscle fibers. This type is the commonest. Numerous delicate fibers branch off and end with small loops or buttons, ensuring a close contact between the nerves and the muscle fibers. The spindles contain numerous, mostly elongated nuclei. Frequently several interconnected spindles are found innervated by a single nerve fiber.

Type 2. Flower-bud-like sensory end-plates. These are also very common (Fig. 3). They are always found in the interstitial connective tissue of the muscles and are not in contact with the muscle fibers. The main, coarse medullated nerve trunk divides into numerous delicate folded branches, which enclose several large plasmatic cells and numerous small nuclei. The entire end-formation is surrounded by capillaries and a connective tissue capsule; the latter is not shown in the illustrations.

Type 3. Arboreal sensory terminations (Fig.4).

Type 4. "Brush-like" sensory end-structures (Fig. 5). Both these structures (Types 3 and 4) are morphologically related sensory types, and both are restricted to the interstitial connective tissue. Between the nerve fibers there are large vacuolated, poorly stained cells which have a distinct central nucleus (Fig. 5). These end-formations are also surrounded by a connective tissue capsule and numerous capillaries. However, the pattern of the network of the nerve fibers is somewhat different: The coarse myelinated fiber of the arboreal type divides into delicate branches resembling that of a tree, while the myelinated fiber of the brush-like variety divides into several relatively coarse branches.

Type 5. Sensory spools (Fig. 6). These formations are built of irregular coils of nerve fibers and contain numerous round or oval nuclei. The entire structure is surrounded by a very delicate connective tissue capsule. Several sensory spools may be seen in the course of a single nerve. These formations are usually seen in the interstitial connective tissue and are less numerous than Types 1, 2, 3, and 4.

Supported by a grant-in-aid from the Department of Health, Education, and Welfare.

From the Laboratory of Neuropathology and Neuro-Ophthalmology, Neuropsychiatric Institute, University of Michigan Hospital.

* References 1, 2, and 3.

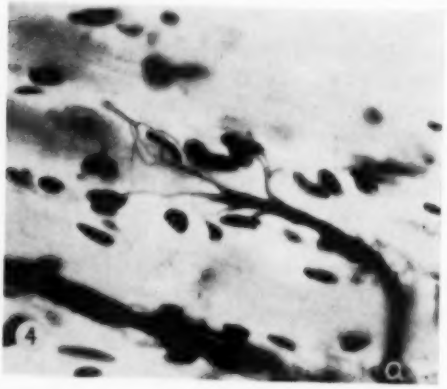
† References 18, 19, and 20.

Fig. 1.—Large sensory spindle of the human eye muscle. The nerve fiber coils around a striated muscle fiber. The spindle is shown in the course of a single nerve (*a-b*). Silver carbonate technique of del Rio Hortega.

Fig. 3.—Large flower-bud-like sensory end-apparatus in the interstitial connective tissue of the human eye muscle: *a*, the main coarse nerve trunk. Silver carbonate technique of del Rio Hortega.

Fig. 2.—Smaller sensory spindle surrounding a striated muscle fiber of a human eye muscle: *a*, the main nerve; *b*, the striated muscle fiber. Silver carbonate technique of del Rio Hortega.

Fig. 4.—Arboreal sensory ending of the human eye muscle in the interstitial connective tissue. The coarse nerve fiber (*a*) divides into delicate branches, resembling the network of a tree. Silver carbonate technique of del Rio Hortega.



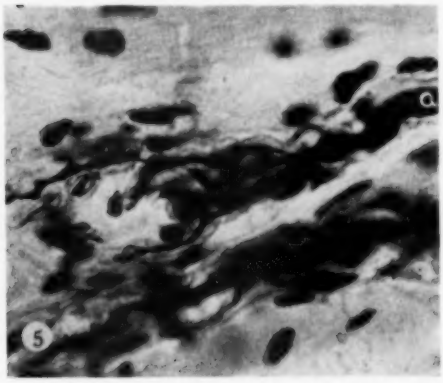


Fig. 5.—Brush-like sensory end-structure of the interstitial connective tissue of the human eye muscle with a large, poorly stained central cell. The main nerve (*a*) divides into several relatively coarse branches. Gros-Schultze method.

Type 6. Sensory end-bulbs (Fig. 7) built of nerve fibers which form a few loosely arranged loops and large vacuolated and pigmented cells. They are surrounded by a very delicate connective tissue capsule. The size of these formations varies greatly, and they are much less numerous than the previously described varieties.

As already mentioned, there are numerous capillaries which surround the buds and the arboreal and brush-like end-organs. These vessels frequently receive a fine fiber which branches off from the coarser nerve trunk and ends on the vessel with a loop or an end-button (Figs. 8 and 9).

Fig. 6.—Sensory spool of the interstitial connective tissue of the human eye muscle. The spool is shown in the course of a single nerve (*a-b*). Silver carbonate technique of del Rio Hortega.

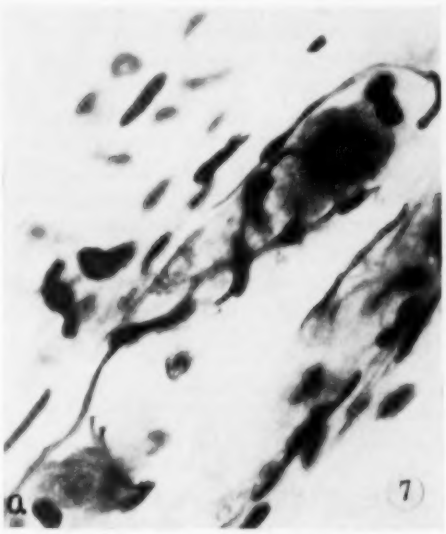


Fig. 7.—A sensory end-bulb of the interstitial connective tissue of the human eye muscle with large pigmented cells in it: *a*, the main nerve. Silver carbonate technique of del Rio Hortega.

There is also a mixed type of end-apparatus which contains two nerves, a motor and a sensory (Fig. 10). The former is placed on a muscle bundle; the latter is in the interstitial connective tissue and is surrounded by a delicate capsule. This end-structure is not an independent variety but a combination of a sensory and a motor structure, previously described.

Much more complicated is the relationship between sensory and vegetative nerves. Frequently very delicate, unmyelinated fibers run near or parallel with coarse, myelinated nerves which form sensory endings of Types 2, 3, or 4, then change their course and run

between the numerous capillaries to end with a loop or an end-button on one of the vessels (Figs. 11 and 12).

The innervations of the six striated muscles which coordinate the movements of the bulb are identical. The levator palpebrae is less richly supplied with nerves.

COMMENT

Sensory end-organs in the striated muscles of the eye have previously been described in animals and in man but have been variously interpreted. Retzius [12] saw these formations in the rabbit and considered them "atypical motor end plates." Huber [6] noted identical structures also in the tendons of the eye muscles of the rabbit but interpreted them as sensory. Dogiel [5] found in the striated muscles of the eye of the horse extensive nerve plexuses, which in his opinion represented sensory systems. Only one of his illustrations shows a sensory muscle spindle in man. This latter finding is in agreement with those of Boecke, Kirsche, and Wolter, who also described those spindles. Woollard [16] noted thin nerves which end in the muscle fibers with small end-bulbs or a delicate network and regarded them as sensory,

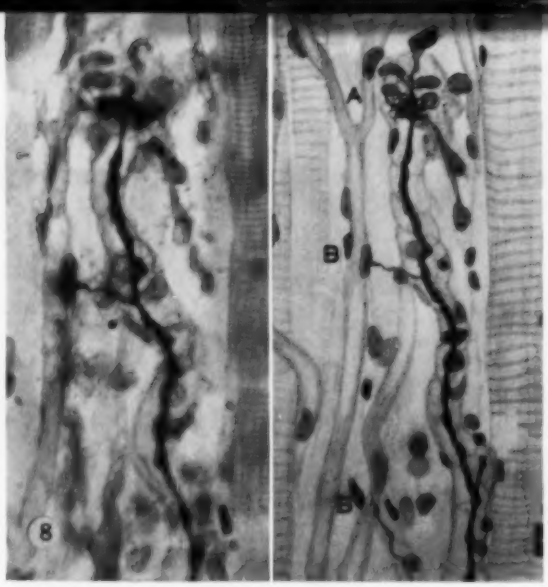
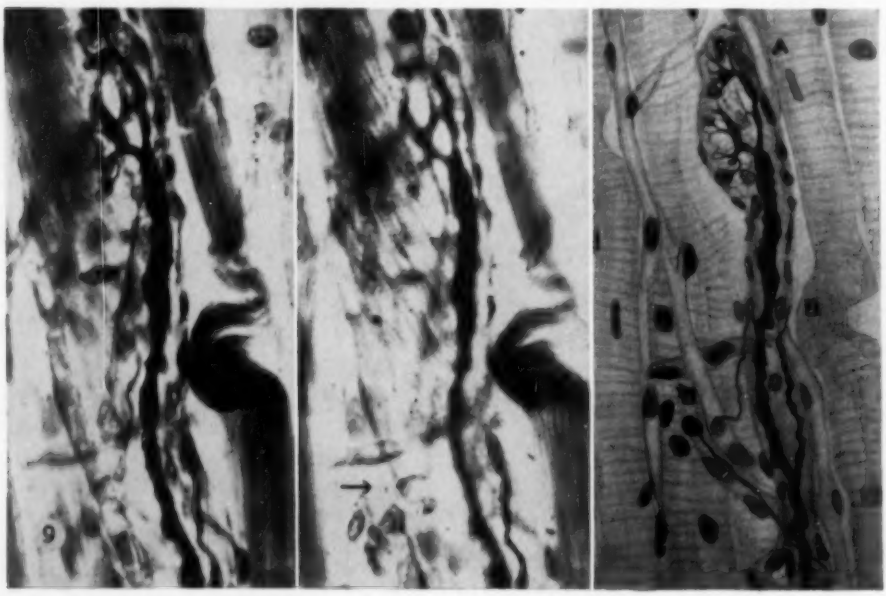


Fig. 8.—Left, photomicrograph and, right, drawing reconstruction of a sensory nerve in the human eye muscle, which sends two fine nerve branches (*B*) to capillaries. The main sensory end-apparatus (*A*) is not quite complete in this section. Gros-Schultze method.

Fig. 9.—Two photomicrographs at different focal planes (left) and one reconstruction by drawing (right) of an arboreal sensory end-apparatus of the human eye muscle (*A*). Three fine nerve fibers branch out of the main nerve (*B*). One of them ends with a loop on a small blood vessel. The body of the nerve branch may be seen in the photomicrograph on the left; the end-loop, on the vessel in the photomicrograph on the right. Gros-Schultze method.



since "they have their origin in the cranial extension of the tractus mesencephalicus of the fifth nerve." Boecke,[2] Kirsche,[9] and Wolter ‡ did not agree with this interpretation and considered these nerve fibers as vegetative in nature.

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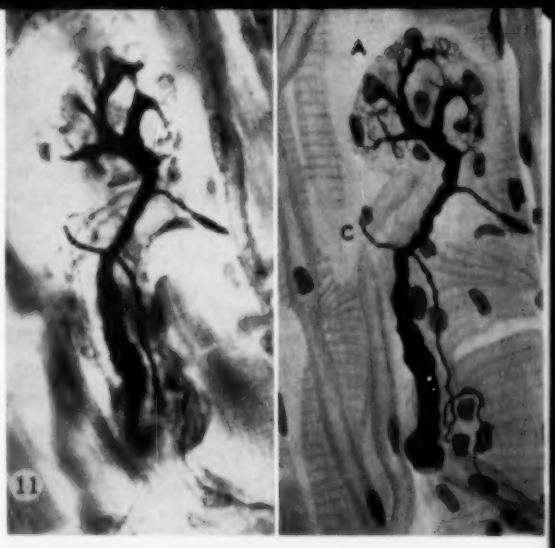


Fig. 11.—Left, photomicrograph and, right, reconstruction by drawing of an arboreal sensory ending (*A*). A nerve fiber branches off the main nerve and ends with a button on a capillary (*B*). Two fine vegetative nerves run together with the coarse sensory nerve, change their course, and run to small blood vessels (*C*). Gros-Schultze method.

Hines [23] with the methylene blue method found "grape-like terminations" in the eye muscle of the rabbit. She interpreted them

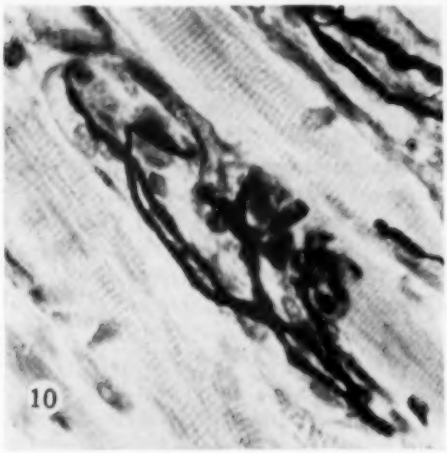
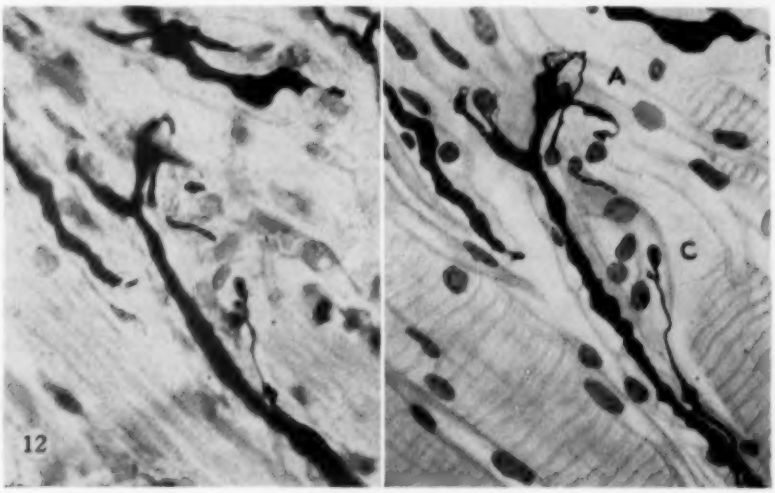


Fig. 10.—A mixed sensory and motor end-apparatus in the human eye muscle. The former is placed in the interstitial connective tissue; it is not quite complete in this section. The latter is in contact with the striated muscle fiber. The main sensory and the motor nerves (right) course together. Gros-Schultze method.

Fig. 12.—A sensory end-apparatus of the human eye muscle may be seen incompletely (*A*). A small vegetative nerve courses with the sensory nerve and ends with an end-button on a capillary (*C*). Left, photomicrograph; right, drawing reconstruction. Gros-Schultze method.



as somatic afferent fibers and identical with the "atypical motor end plates" of Retzius [12] and the "sensory endings" of Huber.[6]

The origin and course of the sensory nerves were investigated experimentally in monkeys by Tozer and Sherrington,[14] who showed that the sensory fibers are carried by branches of the third, fourth, and sixth cranial nerves, and not by the ophthalmic nerve.

Our histological study of the striated muscles of the human eye with the silver

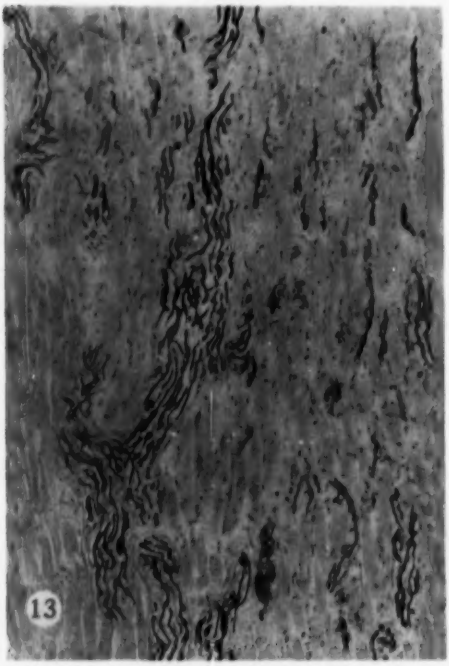


Fig. 13.—Low-power view of the nerves in human superior rectus muscle showing numerous nerve bundles. Gros-Schultze method.

methods of Gros-Schultze and del Rio Hortega shows that the nervous system of these muscles differs substantially from that of the other skeletal muscles, since the eye muscles are characterized by an elaborate system of nerves with various end-formations (Fig. 13).

Sensory nerve endings of Type 1 here described are identical with those seen by Daniel [22] in the muscles of the human eye, which he designated as "simple or multiple spiral nerve endings encircling single muscle fibers." These structures we have called sensory muscle spindles; Boecke [3] (Fig 62, page 303) described identical innervation of the muscle spindle of the intercostal muscle of the hedgehog. Daniel suggested that these nerve endings may be very simple modified muscle spindles, for recording changes in stretch or contraction of the muscles. The structure of complete muscle spindles of the human eye muscle is described by Cooper and Daniel.[21]

Sensory spindles are present in both the muscle fibers and the tendons. Huber [6] first described these spindles in the tendons, which were identical with those in the muscle proper, and concluded that they represented sensory endings. His reasoning is convincing, since motor endings would be useless in the tendons. Similarly, we assume that the end-apparatus of Types 2, 3, 4, 5, and 6 here described are also sensory in character, since these structures were always found in the interstitial connective tissue, and not on or in the striated muscle fibers. Obviously, there is no reason to place motor end-plates in the connective tissue. In addition, there is a distinct morphologic difference in the sensory, motor, and vegetative nerve structures in the human eye muscle.

The presence of sensory spindles suggests that these represent receptors which report the tension of the muscles and tendons. The sensory spools resemble those described by Krause [10] in the subconjunctiva, which, according to Kolmer,[8] represent tactile apparatus.

In summary, there can be distinguished in striated eye muscle sensory, motor, and vegetative nerves with distinctly different end-structures. In previous investigations I have described the motor endings and two different types of vegetative nerves, which we regard as belonging to the sympathetic and parasympathetic systems (Wolter §).

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As described above, there is a very close contact between the sensory nerves and the blood vessels.

The delicate unmyelinated nerve fibers use the sensory end-structures as bridges to reach the capillaries, and we believe that these nerves belong to the vegetative nervous system and innervate the vessels.

SUMMARY

The sensory nerve apparatus of the striated muscle of the human eye forms six types of sensory endings: (1) muscle spindles, (2) flower-bud-like endings, (3) arboreal terminations, (4) brush-like end-structures, (5) spools, and (6) end-bulbs.

Delicate branches of the sensory nerves are intimately connected with small blood vessels. There are delicate vegetative nerves which are associated with end-formations of Types 2, 3, and 4 and which end on the vessels.

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HISTOLOGIC CHARACTER OF CONNECTION BETWEEN BRUCH'S MEMBRANE AND CHORIOCAPILLARIS OF HUMAN EYE

A Study with Silver Carbonate Technique

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KNOWLEDGE of the histologic character of the connection between Bruch's membrane and the choriocapillaris of the choroid is still very limited. A number of older authors (Iwanow,[1] Arnstein,[2] Sattler,[3] Schwalbe,[4] Smirnow,[5] and Wolfrum [6]) investigated various histologic aspects of these membranes in men and animals but failed to explain satisfactorily the morphology of the unusually close relationship which exists between them.

Iwanow [1] stated that the capillaries are so intimately connected with Bruch's membrane by means of delicate connective tissue fibers that a separation is possible only by the use of reagents which dissolve or destroy these fibers. According to Schwalbe,[4] a separation of Bruch's membrane is possible in spite of a very intimate connection, but he admitted that it is very difficult. Sattler [3] and Arnstein [2] confirmed this opinion; none of the authors offered a morphologic explanation of this phenomenon. Smirnow [5] described a connective tissue layer between the membrane of Bruch and the choriocapillaris, which is firmly connected with the fiber network of the latter, but not with Bruch's membrane; he called this connective tissue layer "stratum elasticum supracapillare." Important as his observation is, it failed to explain the extraordinarily strong attachment of Bruch's membrane to the choriocapillaris.

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From the Laboratory of Neuropathology and Neuro-Ophthalmology, Neuropsychiatric Institute, University of Michigan Hospital.

According to Sattler [3] and Wolfrum,[6] Bruch's membrane is divided into two embryologically and anatomically different layers. The inner layer, or basal membrane, is regarded as a part of the pigmented epithelium of the retina, while the outer layer belongs to the choroid. The latter represents the "lamina elastica chorioideae propria" (Lauber [7]). These two layers of Bruch's membrane also are firmly bound together. The inner layer, or basilar membrane, of the pigmented retinal cells is regarded as homogeneous, while the lamina elastica propria contains numerous extremely delicate intertwined connective tissue fibers, some of which occasionally form whorls and send a few delicate fibers into the choriocapillaris (Wolfrum,[6] Lauber,* Duke-Elder [9]).

MATERIAL AND METHODS

Our investigations were carried out on normal human eyes with the silver carbonate method of del Rio Hortega; we utilized the techniques for astroglia and connective tissue (Scharenberg and Zeman [10]). With these techniques we were able to demonstrate the connective tissue structures which form numerous anchors by which both membranes—the choriocapillaris and the membrane of Bruch—are firmly bound together.

HISTOLOGIC EXAMINATION

Figure 1 demonstrates the network of predominantly coarse connective tissue fibers of the human choriocapillaris. This network forms the skeleton of this layer and contains all the other elements: chromatophores, nerves, and blood vessels, but which are not impregnated with the connective tissue technique.

Figure 2 clearly shows the manner in which these coarse fibers stream into the

* References 7 and 8.

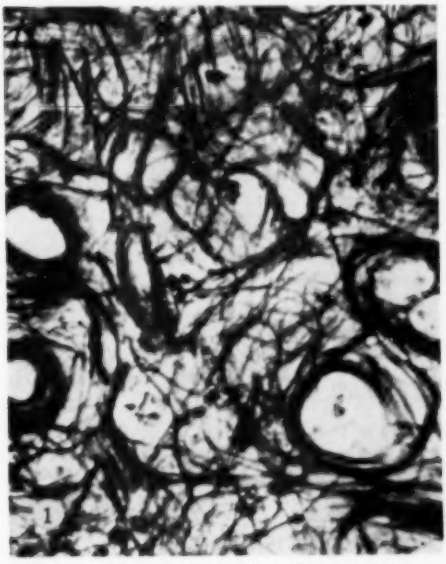
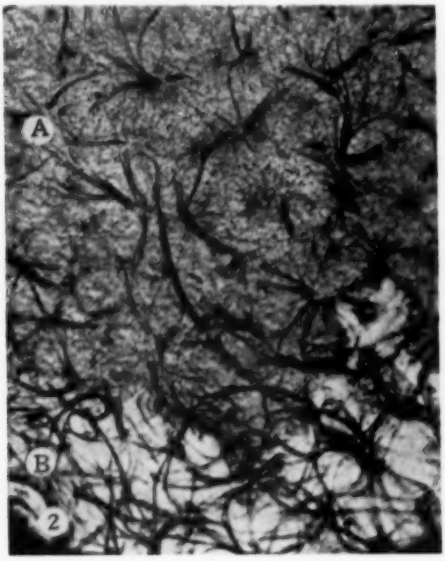


Fig. 1.—Horizontal section of normal human choriocapillaris, with selective impregnation of its coarse connective tissue network. Blood vessels are not impregnated and appear as white spots in the empty rings of fibers. Technique: astroglia variant of del Rio Hortega method; Neofluar; × 253.

Fig. 2.—Horizontal section of the outer layer of the membrane of Bruch (*A*), showing transition to choriocapillaris (*B*). Connective tissue bundles of the choriocapillaris are firmly anchored in the outer layer of Bruch's membrane (*A*). Same technique and magnification as Figure 1.



outer layer of Bruch's membrane (*A*), where they form numerous root- or anchor-like structures.

The structure of the membrana elastica propria (*A*) is shown on Figure 3. It contains a dense intertwined network of delicate

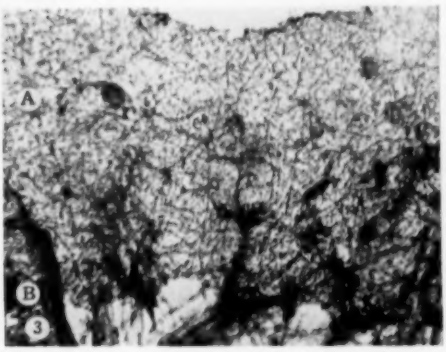
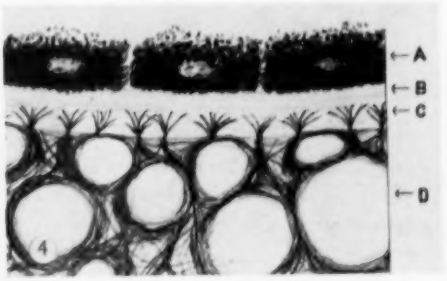


Fig. 3.—Outer layer of Bruch's membrane (*A*) with its delicate network, which serves as a matrix for the coarser connective tissue bundles or anchors. The latter are only partly impregnated. At *B* is the choriocapillaris. Technique: connective tissue variant of del Rio Hortega method; same magnification as Figures 1 and 2.

Fig. 4.—Reconstruction of the histologic details described in this paper. *A*, pigmented epithelium of the retina; *B*, inner layer of Bruch's membrane; *C*, outer layer of Bruch's membrane, with the anchor-like structures; *D*, choriocapillaris.



fibers which serves as a matrix for the above-described connective tissue anchors. The latter were found only in the outer layer of Bruch's membrane, and not in the homogeneous inner layer.

COMMENT

We consider the above-described brush- or root-like connective tissue structures,

which can regularly be demonstrated with silver carbonate, as anchor mechanisms. These fiber bundles penetrate the outer layer of Bruch's membrane as roots of trees penetrate the soil and gain in this manner a firm foothold in the connective tissue network of the membrana elastica. The characteristic structure of these bundles clearly indicates that they are designed as anchors to secure a particularly close and durable contact between the choriocapillaris and Bruch's membrane. The delicate fibers of this membrane, to which Wolfrum called attention, serve as a firm matrix for the penetrating fiber bundles here described.

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MELANOBLASTS OF THE NORMAL HUMAN CHOROID

Study with Silver Carbonate and Silver Nitrate

J. REIMER WOLTER, M.D., Ann Arbor, Mich.

THE MELANOBLASTS constitute an important element of the choroid of the human eye, but their morphology and physiology have attracted little attention; they are generally considered as elements without particular function and of limited biologic significance, destined only to fill out the space. That such a view is not justified can be demonstrated with modern silver methods, which disclose an intricate relationship between the melanoblasts and other elements of the choroid; this relation suggests that these pigmented cells have important functions.

MATERIAL AND METHODS

The tissue examined was that of normal human eyes. Figures 1 to 7 were prepared with the silver carbonate method of del Rio Hortega without reduction (Scharenberg and Zeman [1]). This technique permits a complete impregnation also of those segments of processes of the melanoblasts that, according to Lauber,[2] contain only colorless premelanotic pigment. This substance stains black with colloid silver, so that all parts of the processes stand out distinctly. Figure 8 was prepared with the modified technique of Gros-Schultze to demonstrate the relationship between melanoblasts and pericytes, and Figure 9, with the connective tissue technique of del Rio Hortega (Scharenberg and Zeman [1]), which demonstrates the melanoblasts and the connective tissue network in different hues.

HISTOLOGIC DESCRIPTION

The density of the melanoblasts varies in different layers of the choroid: In the suprachoroid, also called epichoroid, these cells are very numerous; their pattern is compact, and they fill out completely all the space between the vessels, the nerves, and the connective tissue network (Fig. 1); toward the choriocapillaris (also called capillary layer) the pattern gradually changes into a delicate network of long, slender, branched-out elements (Fig. 2).

There is also a great morphologic difference between the melanoblasts in the various layers of the choroid: In the suprachoroid the cells are large, coarse, and with thick, plump processes (Fig. 1); in the middle layers they are approximately star-shaped (Figs. 3 and 9), and in the choriocapillaris, as above-mentioned, delicate, slender, and branched forms prevail (Figs. 2, 7, and 10).

The melanoblasts form a three-dimensional network or plexus with large meshes in the choriocapillaris (Figs. 2 and 7), syncytial in character, which is arranged predominantly parallel to the retina, so that horizontal sections supply the most valuable information.

In all layers of the choroid there is a very intimate and characteristic relationship between the melanoblasts and the blood vessels. In the outer layers the large and coarse cells form dense perivascular sleeves (Figs. 1 and 10), but in the middle layers the histologic picture is fundamentally different: The melanoblasts here are predominantly star-shaped and are attached to the vessels by numerous processes (Figs. 3 and 10), which frequently end with foot-like structures among the pericytes (Fig. 8). In the choriocapillaris and in the layer of the small vessels (classification after Duke-Elder [3]) the melanoblasts appear as slender cells with a distinct round or oval nucleus and long processes which terminate with delicate branches upon the vessel wall (Figs. 4 and 10).

There is also a very close relationship between the melanoblasts and the nerves of the choroid: In the outer layers the coarse

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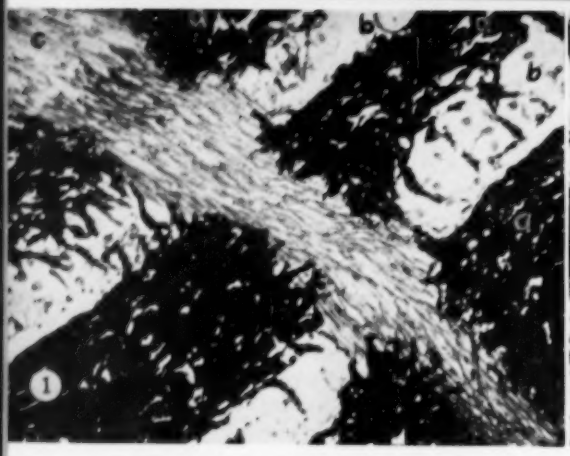
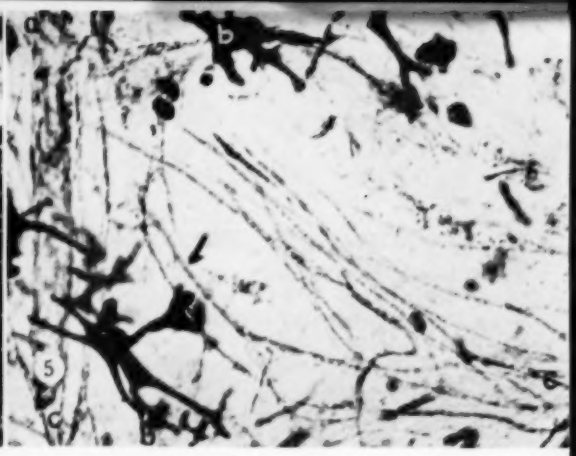
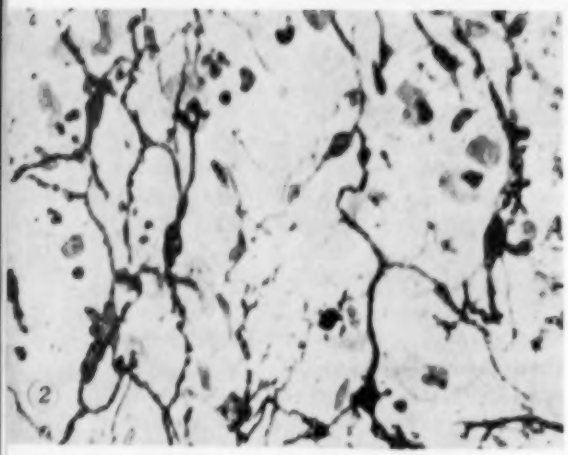
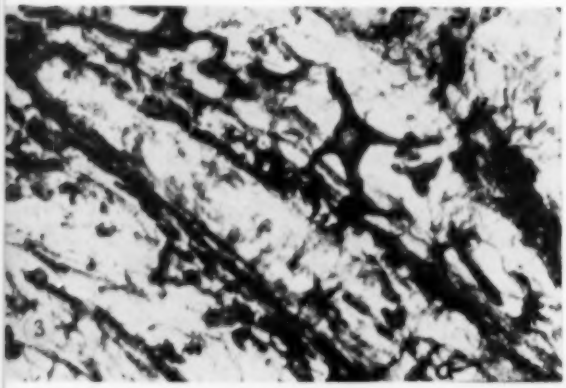
From the Laboratory of Neuropathology and Neuro-ophthalmology, Neuropsychiatric Institute, University of Michigan Hospital.









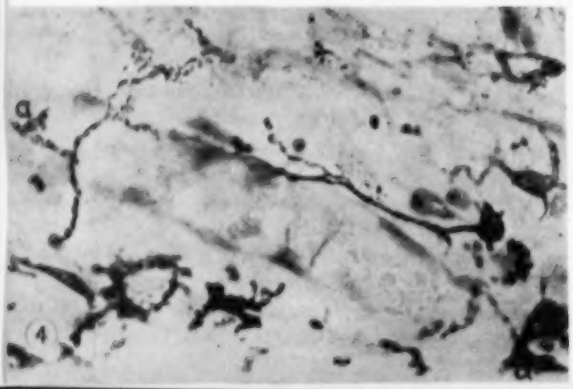


Fig. 1.—Horizontal section of the layer of the large vessels of the human choroid: (*a*) dense network of melanoblasts; (*b*) large blood vessels, (*c*) a coarse nerve bundle. Hortega method; Apochromat; × 13.3.

Fig. 2.—Loose network of slender melanoblasts of the human choriocapillaris. Horizontal section; del Rio Hortega method; fluorite; × 26.6.

Fig. 3.—Star-shaped melanoblast ending with two foot-like structures on a middle-sized vessel of the choroid (*a*). Hortega method; fluorite; × 26.6.

Fig. 4.—Slender melanoblast of the layer of the small vessels, which ends with a long-branched process on a blood vessel (*a*). Hortega method; fluorite; × 26.6.

Fig. 5.—Human choroid with small blood vessels (*a*) and star-shaped melanoblasts (*b*), with processes which end among the fibers of the dense nerve plexus (*c*). Hortega method; fluorite; × 26.6.

nerve bundles are surrounded by dense masses of melanoblasts in a manner similar to the arrangements around the large blood vessels of this area (Fig. 1); in the inner layers, which contain numerous nerve plexuses, the contact between melanoblasts and nerve fibers is very intimate, and numerous processes of the former can be seen between the nerve fibers (Fig. 5). The neurons of the choroid are usually surrounded by melanoblasts, which seem to serve as satellites to the nerve cells, in a manner similar to that of the glia (Fig. 6).

As already outlined, there are only a few melanoblasts in the choriocapillaris; but there are always some present, and they are frequently seen in the space between the capillaries (Fig. 7). Occasionally their processes seem to be in contact with Bruch's membrane.

The entire system of melanoblasts rests on a skeleton of connective tissue fibers, which also supports the blood vessels and nerves of the choroid (Fig. 9; Wolter [3]).

COMMENT

The histologic findings here outlined strongly suggest that the melanoblasts of the human choroid are not simply cellular structures filling out the space among the vessels, but represent a complicated system by means of which a close contact is established between the blood vessels and the nerve structures. It is therefore reasonable to assume that this network of melanoblasts is charged with important functions in regulating the metabolism of the retina. The histologic pattern of melanoblasts of the choroid is to some extent, at least, similar to that of the astroglia in the retina and in the central nervous system in general.

As demonstrated in Figure 8, there exists a complicated relationship between the mel-

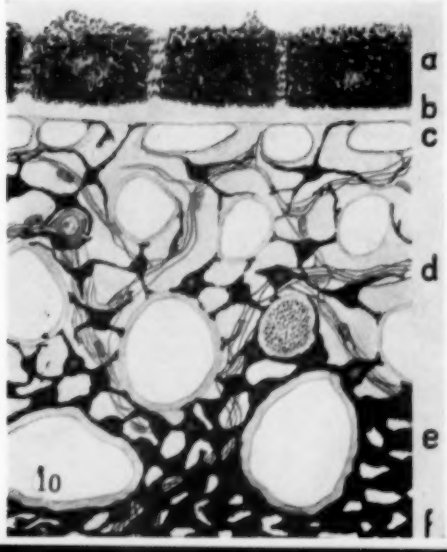
Fig. 6.—Melanoblasts of the human choroid surrounding a ganglion cell. The latter is recognizable by the typical nucleus; the cell body is not impregnated. Hortega method; fluorite; × 26.6.

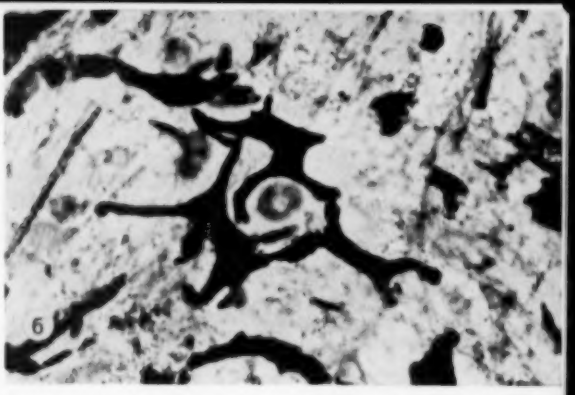
Fig. 7.—Slender melanoblasts of the human choriocapillaris (*b*); the capillaries may be recognized by the rows of black-stained erythrocytes (*a*). Hortega method; fluorite; × 26.6.

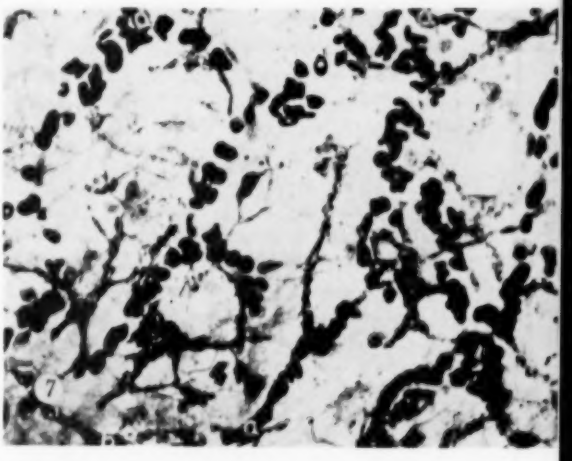
Fig. 8.—Melanoblast of the human choroid which ends with a foot-like structure (*a*) upon the wall of a small blood vessel (*b*), among numerous large pericytes. Gros-Schultze technique; fluorite; × 26.6.

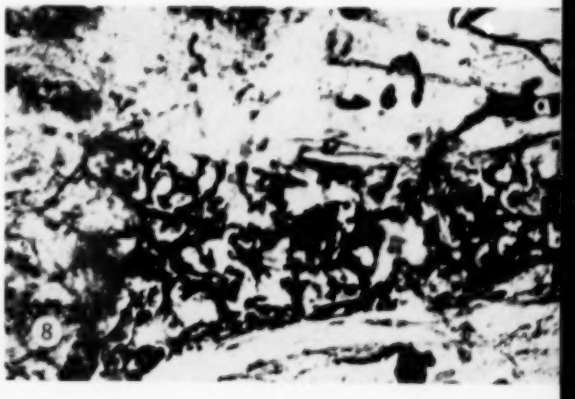
Fig. 9.—Star-shaped melanoblasts (*a*) of the layer of the large vessels supported by the connective tissue network (*b*) of the choroid. Hortega method; fluorite; × 26.6.

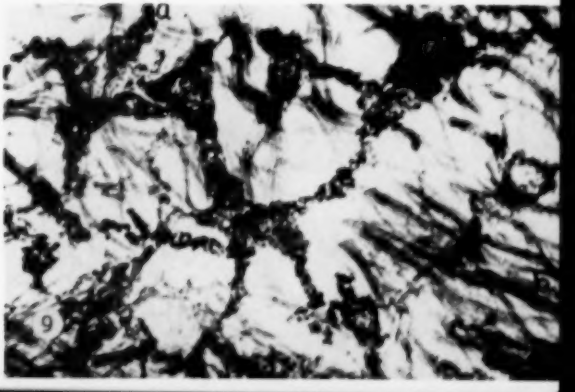
Fig. 10.—Reconstruction of the histologic findings here illustrated: (*a*) layer of the pigmented cells of the retina; (*b*) Bruch's membrane; (*c*) choriocapillaris; (*d*) vascular layer of the small vessels; (*e*) vascular layer of the large vessels; (*f*) suprachoroid.











anoblasts and the pericytes (Rouget,[5] Zimmermann,[6] Schaly [7]) of the vessel wall; this will be the object of a separate investigation, to be published in the near future.

Münch [8] is of the opinion that the choroidal melanoblasts are of "muscular nature"; we found no signs of "muscle-like structures" and are not able to confirm Münch's theory.

Fundamental descriptions of the histology of the melanoblasts of the choroid have been published by Lauber,[2] Wolfrum and Lauber,[9] Duke-Elder,[4] Bargmann,[10] and Friedenwald and associates.[11]

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ULTRASONIC WAVE LIQUEFACTION OF VITREOUS HUMOR IN LIVING RABBITS

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ONE APPROACH to the problem of the treatment of vitreous hemorrhage is based on the assumption that the breakdown products of blood will diffuse more readily, and thus be absorbed more quickly, in a fluid vitreous than in a gel-like vitreous, the viscosity of which hinders diffusion. Although such an assumption is reasonable, it has never been rigidly tested, partly because there is no technique at present for liquefying the vitreous without injecting into the eye injurious substances.

The literature on ultrasonic radiation suggests a possible means of liquefying the vitreous without causing concomitant inflammation.* In addition, previous studies have shown that red blood cells suspended in saline are destroyed by ultrasound. Although this poorly understood energy form has as yet found no clear-cut ophthalmological uses, certain promising facts have emerged from the experimental work. It has been reported by several groups of investigators that ultrasound can liquefy the excised vitreous. Further, it has been shown that, despite injurious effects, such as cataract formation by ultrasound at high intensity, ocular tissue can tolerate this radiation within certain limits. In a number of cases human eyes were treated with ultrasound without reported damage.

In view of these findings, the present work was undertaken to study the effect of ultrasound on the intact vitreous and to develop, if possible, a technique for selectively liquefying the vitreous in living animals.

BACKGROUND AND GENERAL METHOD

Ultrasonic waves are by definition sound waves whose frequency is greater than 18,000 to 20,000 cycles per second (cps). Though usually generated by high-frequency electric oscillators, ultrasound is a purely mechanical phenomenon, and as such is not related to microwaves, diathermy, or radar. At frequencies of 1,000,000 cps, however, ultrasound acquires some properties that are not shared by sound. For instance, ultrasound, with its high frequencies and short wave length, may be accurately reflected and focused in a manner similar to light. Secondly, ultrasound is readily absorbed by some substances, and this absorbed energy is transformed into heat. Thus, ultrasound may be used for selective heating. Thirdly, when ultrasound is propagated through a substance, minute particles of the substance are subjected to large alternating changes in pressure; at high intensities these alternating changes in pressure may actually rip open the propagating substance and cause minute cavities to appear. The rapid appearance of these cavities is called "cavitation," and this process accounts for much of the destructive action of ultrasound.

In the present investigation ultrasonic waves were generated by connecting a high-frequency electric oscillator to one of several piezoelectric crystals. The electric oscillator

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The studies on traumatic hemorrhage in the vitreous, of which this paper is a part, are based on work performed under Contract #DA-49-007-MD-273 of the Department of the Army.

* References 1 to 17.

was built to specifications. Its output varied from 0 to 90 watts. Its frequency could be varied from 600,000 to 8,000,000 cps.

Characteristics of two of the piezoelectric crystals are listed in the accompanying Table. In some experiments small flat crystals were used; these generate plane ultrasonic waves. In other experiments curved crystals were used; these have the advantage that they focus the ultrasound. It was possible to calculate within broad limits the location and theoretical dimension of the focal core.[18] The sonic output for each of these piezoelectric crystals was determined by measuring the sound radiation pressure impinging upon a piece of Ro C rubber, according to a method described by Willard.[19] By dividing the sonic output by the area of either the crystal face or the focal core, the intensity of the ultrasonic wave at the crystal face or in the focal core was estimated. It should be emphasized that there are many experimental and theoretical sources of error in such a method of measuring ultrasonic intensity. The data on intensity, then, should be interpreted more as an order of magnitude than as a precise value.

Vitreous humor was obtained from the eyes of cattle killed several hours before the experiment; the eyes were kept at a temperature of approximately 4 C. prior to their use. In one series, of 25 experiments, the vitreous was dissected from the eye and placed either in a small glass bottle (15 experiments) or in a very thin transparent plastic sack (10 experiments); in another series, of 20 experiments, the vitreous was left intact in the eye and the entire eye was exposed to the ultrasound.

For each transducer the voltage across the crystal face was correlated with the actual acoustic intensity, as measured by sound radiation pressure. Thus, one could translate a voltage reading directly into the intensity of the ultrasonic waves.

Characteristics and Operating Output of Two Barium Titanate Transducers

Description	Surface Area, Sq. Cm.	Frequency, Megacycles	Maximum Total Output, Watts	Maximum Intensity at Crystal Face, Watts/Sq. Cm.	Maximum Intensity at Focal Core, Watts/Sq. Cm.
Concave disc with central opening. Radius of curvature, 30.0 mm.; chord diameter, 50.0 mm.	24.0	1	70	3	900
Flat disc	3.7	2.7	44	12	12 (no focus)

IN VITRO EXPERIMENTS

Materials and Methods.—A fish tank was fitted with a removable side so that one of several barium titanate transducers could be mounted at one end. The tank was filled with water, and the transducer was connected by an appropriate impedence-matching coil to the electric oscillator. The specimen, fixed in a clamp attached to a ring stand, was held directly in the path of the ultrasonic waves (Fig. 1).

Results.—When the excised vitreous was placed in a glass bottle and then exposed to plane ultrasonic waves of an intensity of approximately 12 watts per square centimeter, irreversible liquefaction of the vitreous ensued within three to five minutes. This liquefaction was always preceded by the sudden appearance of many minute bubbles scattered diffusely throughout most of the vitreous substance. As the radiation continued, these bubbles increased in size and agitated vigorously until the vitreous was rendered completely fluid.

When the glass-enclosed vitreous was placed at or near the focal point of the large curved transducer, which was emitting 2 watts per square centimeter at its surface, irreversible liquefaction occurred in a similar manner. Even under these circumstances the liquefaction did not appear to originate at a specific area but occurred after the sud-

den appearance of minute bubbles scattered diffusely throughout the vitreous. If the intensity of the large focusing transducer was reduced, liquefaction of the vitreous still occurred but the process took longer. (No attempt was made to correlate the intensity of radiation with the time necessary to achieve liquefaction because it was difficult to determine objectively when the vitreous was completely fluid.)

The temperature of the vitreous humor in the preceding experiments was measured by placing a thermometer in the vitreous immediately before and after liquefaction; the rise in temperature was usually about 4 C. By interrupting the ultrasonic radiation, liquefaction was achieved with a temperature

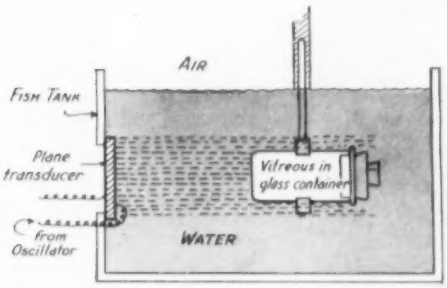


Fig. 1.—Diagrammatic sketch of apparatus used to expose vitreous body in vitro to plane ultrasonic waves.

rise of the vitreous of not more than 1 degree C. Lowering the temperature of the vitreous to 6 C. did not interfere with the ultrasonic liquefaction.

In three instances micro-Kjeldahl nitrogen determinations were performed on the insoluble vitreous protein obtained by high-speed centrifugation. There was no significan difference in the amounts of insoluble protein nitrogen per gram of vitreous in the ultrasonically liquefied vitreous and in the control vitreous. In three cases the amount of hyaluronic acid was measured by determining the hexuronic acid content of the ethanol precipitate; as in the previous instance, the amount in the control vitreous and that in the ultrasonically liquefied vitreous did not differ significantly.

When the vitreous placed in a thin-walled plastic sack, instead of a rigid glass bottle, was exposed to ultrasonic radiation, no liquefaction resulted. Even when the ultrasonic intensity was raised to the maximum obtainable with our apparatus (900 watts per square centimeter at the focus of the large focusing crystal) and maintained for 30 minutes, no liquefaction occurred. Similarly, when the intact eye was held directly in the path of ultrasound, liquefaction could not be accomplished despite radiation at maximum intensities. In these cases the temperature of the vitreous increased by 20 or 30 degrees, but no disruption of the vitreous gel was observed.

Comment.—The foregoing results appear paradoxical: Ultrasound readily liquefied vitreous held in a glass container, but even very high ultrasonic intensity did not liquefy vitreous contained in a thin plastic sack or in the intact eye. Glass is a partial reflector of ultrasonic waves, and the vitreous in a glass container is subjected to ultrasonic standing wave patterns reflected from the walls of the container, whereas the plastic sack and the tunics of the eye are, theoretically, poor reflectors of ultrasound and, therefore, minimal standing waves are set up; this may explain to some extent the disparity of results. However, in all probability, this explanation is incomplete, for the calculated intensity of the ultrasound at the focal core is about 1 kw. per square centimeter, and it is unlikely that standing waves can augment the intensity of plane waves of 15 watts per square centimeter to this level.

In two earlier reports† the liquefaction of the vitreous was described as an incidental finding. In these experiments the vitreous was irradiated in vitro and held in a partially reflecting container. No mention was made of inability to liquefy the vitreous in the intact eye. Grün and co-workers[7] reported the use of plane ultrasonic waves of low intensity to liquefy both excised vitreous and the vitreous in the intact eye. In this study the authors observed that by cutting a fistula

† References 1 and 15.

in the back of the eye or by injecting air into the vitreous they increased the extent of liquefaction. There was, however, the clear implication in these experiments that ultrasound of low intensity did cause some liquefaction of the undisturbed vitreous in the intact eye, even without these modifications.

IN VIVO EXPERIMENTS

It was evident from the initial results of this investigation that direct application of ultrasonic radiation to the eye, even with intensities as high as 1,000 watts per square centimeter, does not induce vitreous liquefaction. Apparently, this effect is achieved only when the ultrasonic waves are reflected, thus setting up standing wave patterns. Under these conditions liquefaction occurred with intensities as low as 15 watts per square centimenter. Therefore a method was devised in which an air bubble was introduced into the vitreous and served as a reflecting surface, thereby setting up standing wave patterns in the living rabbit's eye.

Technique.—In a series of more than 30 experiments, adult rabbits were anesthetized with intravenous pentobarbital (Nembutal) and subconjunctival dibucaine (Nupercaine). Paracentesis of the anterior chamber was performed in order to allow for the injection of 0.4 cc. of air into the vitreous cavity. After paracentesis, the rabbits were given heparin intravenously so that fibrin nets could not develop in the anterior chamber and obscure visualization of the interior of the eye. The rabbit was placed on its side so that the eye to be treated faced directly downward, and the injected air then "floated" up toward the posterior pole of the eye. The rabbit was held in this position by an adjustable ratchet-and-pinion device, which made it possible to adjust the animal's head in a vertical direction. A curved focusing transducer was sealed into an aperture in the center of a Lucite pan (Fig. 2). This transducer had an 8 mm.-bore hole, in the center of which a microcoverslip was cemented. This entire assembly could be moved in any horizontal direction. The pan was filled with liquid petrolatum U. S. P. and the rabbit's head lowered and positioned so that the pupil was aligned with the opening in the transducer. The liquid petrolatum occupied the space between the transducer and the rabbit eye.

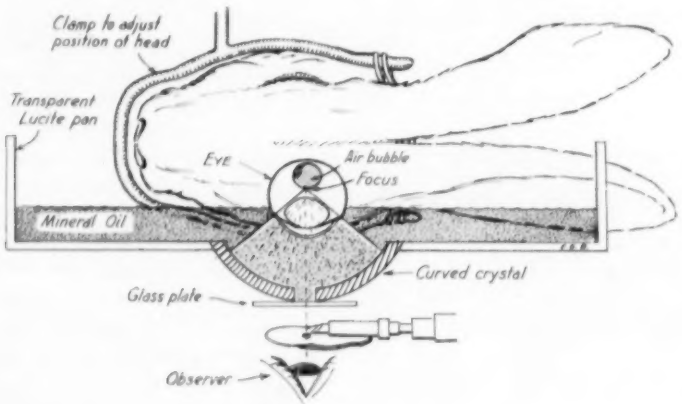


Fig. II.

Fig. 2.—Diagrammatic sketch showing relative positions of observer's eye, focusing transducer, focus, and rabbit eye with injected air bubble.

With this arrangement, it was possible to view the air bubble ophthalmoscopically through the bore hole in the transducer and to observe characteristic changes effected by the sound waves. At the same time the ap-

paratus was manipulated vertically so that the focal core impinged at the air-vitreous interface, and horizontally so that the focal core was exactly centered on the bubble. When these adjustments were made correctly, ultrasonic waves, even of low intensity, left the face of the crystal, passed through cornea, iris, lens, and anterior portion of the vitreous, and converged to a focus of high intensity at the air-vitreous interface.

At any given intensity the radiation was performed in an intermittent manner; exposure was interrupted every two seconds by an equivalent silent period in order to minimize the accumulation of heat. The exact amount of heat reduced by this procedure was not measured, but it was observed that lightly anesthetized animals tolerated this form of radiation for 20 to 30 minutes without moving, whereas animals subjected to constant radiation of the same intensity jerked their heads away in 2 to 3 minutes.

A rough, but reproducible and objective, technique served for assessing the liquefaction of the vitreous: The excised eye was placed in an upright position; the cornea and iris were removed, and the zonular fibers were severed carefully to free the lens. In control eyes, the lens, supported by the normal vitreous and injected air, remained in position and even resisted gentle efforts to push it down toward the posterior pole of the eye. In eyes in which the vitreous had been liquefied by ultrasound, injected air escaped, the unsupported lens immediately sank to the bottom of the preparation, and fluid vitreous extruded over the edges of the sclera.

Results.—Ultrasonic waves focused on the surface of an injected air bubble consistently liquefied the vitreous humor of living rabbits. As the acoustic power emanating from the crystal gradually increased, a small shallow depression developed on the surface of the air bubble where the sonic waves came to a focus. This depression became deeper, and the entire bubble was seen to vibrate as the intensity was increased to 1.5 watts per square centimeter at the crystal face (Fig. 3). After one to five minutes of intermittent radiation at this intensity the vitreous humor became substantially liquid. The sudden appearance of minute bubbles in the vitreous substance always preceded this liquefaction. These minute round bubbles were apparently caught in the standing waves between the transducer and the reflecting air bubble. They agitated violently throughout the vitreous during each period of radiation. In order to obtain maximum liquefaction, it was necessary to irradiate for a total of about 10 minutes after the appearance of the small bubbles. However, some liquefaction did occur even after irradiation was discontinued, immediately after the appearance of the fine bubbles. If the vitreous was liquefied, one could observe the small round bubbles floating in its substance. They numbered 10 to 200, and were often clumped in groups of 5 to 10. The amount of liquefaction induced in the vitreous corresponded roughly to the number of the bubbles. These minute bubbles were distinct from the large reflecting air volume, which was still intact and was to be seen at the uppermost portion of the eye. Between the small bubbles even markedly liquefied vitreous remained clear, and no pathologic changes of the retina could be seen with the ophthalmoscope. After treatment smaller irregular opacities, difficult to detect, appeared in the vitreous. These seemed to coalesce in time.

Twenty-four hours after the irradiation the vitreous showed striking changes. Numerous large, grayish-white, granular membranes and strands, which were easily seen with focal illumination or with the ophthalmoscope, had formed throughout the vitreous. Gentle tapping of the globe caused these membranes and strands to undulate in fluid vitreous. The extent of strand formation paralleled the degree of vitreous liquefaction. In some eyes with moderate liquefaction of the vitreous only a few membranes were present, whereas in eyes with fluid vitreous membranes and strands formed a dense network, which appeared to radiate from dense, white granular clumps.

Slit-lamp examination of the liquefied vitreous after extracapsular removal of the lens revealed that these strands and nets were composed of numerous irregular, opaque granules or, in other instances, of opaque fibrous elements, in varying degrees of coalescence. Paracenteses and air injections produced, in control eyes, only a rare, small granular opacity in the vitreous.

Histologic examination of these eyes showed solid vitreous of normal microscopic structure, solid at the vitreous base and in front of the optic nerve. The remainder of the vitreous was changed into a more or less homogeneous granular-appearing structure, indicative of liquefaction. The extent of the change varied according to the amount of irradiation. In some areas large, intensely

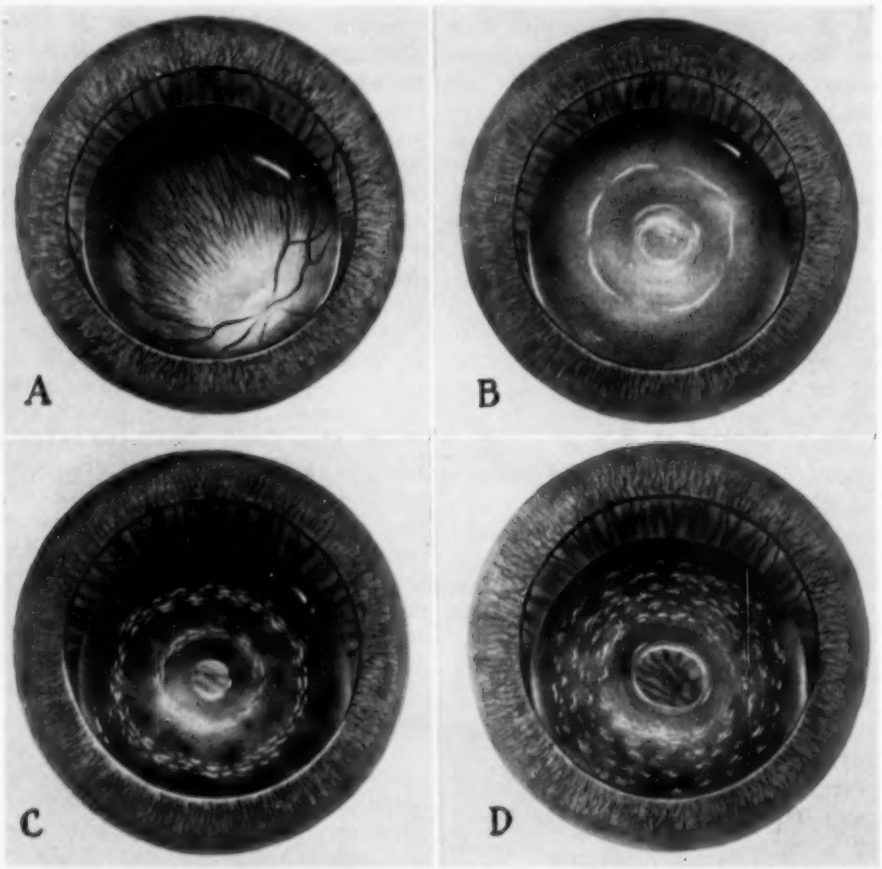


Fig. 3.—Semischematic illustration of ophthalmoscopic view of rabbit eye after injection of 0.4 cc. of air into the vitreous body.

A, air bubble as it appears before onset of irradiation.

B, indentation caused by the focal core of ultrasonic waves seen in center of air bubble.

C, deeper invagination of the surface of the air bubble as a result of higher intensities of focal ultrasonic waves. At this stage the entire bubble vibrates.

D, hole "drilled" through bubble by high-intensity ultrasonic waves, exposing the retina to the radiation.

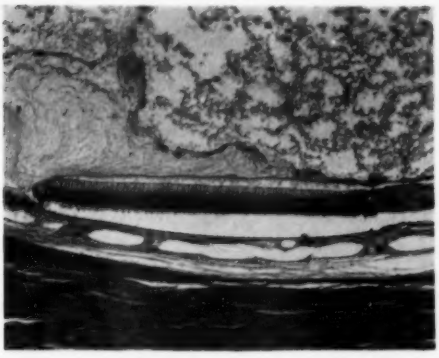


Fig. 4.—Section near ora serrata of rabbit eye, showing widespread disorganization of the vitreous, indicating that the ultrasonic waves caused liquefaction. Base shows normal architecture, and underlying retina appears normal except for localized area of injury. Hematoxylin and eosin stain.

stained eosinophilic fibers were connected with fragments of various sizes. Morphologically they appeared to correspond to the granular membrane seen with the ophthalmoscope. It was not possible to ascertain histologically whether these fibers were denatured vitreous protein or fibrin.

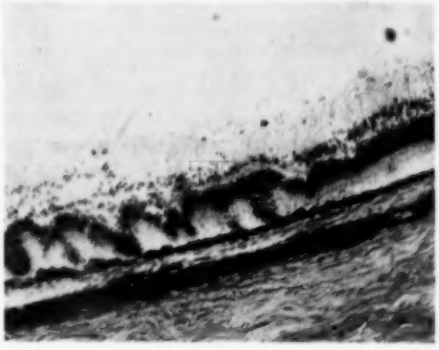
Several of the eyes in which the vitreous had been liquefied were observed for three months. The signs of inflammation from the air injection disappeared after a short time; the eyes then remained white, the corneas clear, and the anterior chambers free of pathologic changes. The dense vitreous strands, however, gave no indication of progressing or regressing during this period, and the vitreous showed no tendency to resume its gel-like state.

Aside from the changes in the vitreous, the only ophthalmologically demonstrable signs of ocular damage consisted of minute vacuoles, which appeared in front of the posterior lens capsule in a localized area. These vacuoles resembled those described by Schwab,[20] and also by Lavine,[15] who termed them "reversible cavitation." In the present experiment, on living animals, these vacuoles persisted without change for the several months during which the animals were observed. Because of the small number and size of these vacuoles they did not interfere with the visibility of the eyeground.

Although ophthalmoscopically the fundus appeared normal, histologic examination disclosed extensive retinal damage of a characteristic pattern (Figs. 4 and 5). The lesions consisted of many sharply limited areas of acute angular displacement of the nuclei of the outer granular layer toward Bruch's membrane, interposed between and adjacent to many areas of apparently completely normal retina. In some areas the passage of ultrasound apparently did not disrupt any of the structures in front of the foci of displaced elements in the outer nuclear layer. In other areas, the damage was particularly great, the inner and outer nuclear layers were fused, and their elements were pushed toward Bruch's membrane, with destruction of the neuroepithelium. In these parts there was evidence of nuclear fragmentation. In most cases the retina near the optic disc showed minimal signs of injury. This area, several disc diameters in width, corresponded to the part of the tissue protected by the middle portion of the injected air bubble.

Comment.—The observations on living rabbits confirm the results obtained from the experiments on vitreous body in vitro and clearly demonstrate that ultrasonic waves, when focused at the air-vitreous interface under the described experimental conditions, induce liquefaction of the gel. However, ultrasonic waves applied according to the present technique caused three untoward

Fig. 5.—Retinal damage induced by ultrasonic radiation. Nuclear layers in many areas are displaced sharply outward. Hematoxylin and eosin stain.



effects in the intact eye, namely, the development of small vacuoles in the posterior lens cortex, bizarre retinal lesions, and the formation of strands in the vitreous.

The question arises as to whether these deleterious effects can be avoided by refinements in technique. The small lens vacuoles are, in all likelihood, the result of cavitation. More accurate control of the intensity and more accurate focusing might eliminate this damage. It should be noted that, because of the geometry of the rabbit eye, with its relatively small vitreous space, the lens is more directly exposed to the reflected radiation. It could also be argued that more precise focusing would prevent these retinal lesions which arise when the focal core of the ultrasound waves is deflected obliquely from the air bubble; if the high intensity sound were reflected directly back toward the crystal, the retina would be spared, an assumption which is supported by the observation that damage to the retina is minimal directly behind the bubble and severest on each side.

On the other hand, the development of dense opacities in the vitreous after liquefaction depends more upon responses of the hydrogel per se to the ultrasonic waves than upon techniques of application. It is unlikely that any alteration in the method would prevent the development of these strands in the vitreous following mechanical liquefaction. Therefore, although it may be possible to render the vitreous liquid without inflicting damage to any other ocular structures, the opacities which develop in the vitreous itself after ultrasonic irradiation offset any advantages inherent in the vitreous liquefaction.

SUMMARY

A method of inducing liquefaction by application of ultrasound to vitreous humor of steer eyes in vitro and rabbit eyes in vivo was developed. The conditions necessary for such liquefaction were investigated.

The results suggest the following conclusions:

(*a*) The liquefaction is not due to heat accumulation.

(*b*) No significant decrease in insoluble vitreous protein or in vitreous hyaluronic acid occurs in those vitreous bodies liquefied by ultrasound.

(c) Liquefaction is a mechanical phenomenon: The sound waves provoke the formation of minute bubbles, probably due to cavitation, and the subsequent growth and violent agitation of these bubbles disrupt the vitreous structure.

A short time after ultrasonic liquefaction of the vitreous in living rabbits, many dense white strands and membranes appeared in the vitreous cavity. During the observation period of several months they persisted without change.

As a result of ultrasonic irradiation with the technique employed, two injurious effects on other ocular tissues were demonstrable.

(*a*) In the lens, minute vacuoles, which had not changed at the time the experiment was terminated, appeared in the posterior cortex.

(*b*) The retina, despite a normal ophthalmoscopic appearance, showed histologically extensive lesions of a characteristic nature.

Dr. Ludwig von Sallmann, of the Department of Ophthalmological Research, Columbia University College of Physicians and Surgeons, gave constructive criticism and guidance in this study, and Mr. G. W. Willard, of the Bell Laboratories, contributed advice on the problems of the physics of ultrasound.

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News and Comment

SOCIETY NEWS

Canadian Ophthalmological Society.—The 17th Annual Meeting of the Canadian Ophthalmological Society was held at the Physical Sciences Centre, McGill University, Montreal, in September, 1954. Dr. Mark Robert Marshall was in the chair.

This being the year of the International Congress of Ophthalmology, the meeting of the Canadian Ophthalmological Society was transferred from the usual meeting time, in June, to just before the Extension of the International Congress, held in Montreal on September 10 and 11. On account of this we had the largest attendance of visitors that we have ever had. This was the source of great pleasure and satisfaction to the members of the Canadian Ophthalmological Society.

The scientific program was abbreviated and consisted of nine papers. Prominent among these were those of our two guests of honor. Dr. John H. Dunnington, of the Institute of Ophthalmology, Presbyterian Hospital, New York, spoke on "Defective Ocular Wound Healing: An Experimental and Clinical Study," and Prof. G. B. Sourdille, of Nantes, France, spoke on "Lamellar Keratoplasty." The papers of both these distinguished ophthalmologists will appear in the *Transactions of the Canadian Ophthalmological Society*.

Dr. Dunnington and Prof. Sourdille were elected Honorary Members of the Society.

Dr. Percy B. Macfarlane, of Hamilton, Ontario, was elected president for the coming year, while Dr. Henri Pichette, of Quebec City, was elected vice-president. The secretary, Dr. R. G. C. Kelly, of Toronto, Ontario; the treasurer, Dr. J. V. V. Nicholls, of Montreal, and the editor-in-chief of the *Transactions*, Dr. Clement McCulloch, of Toronto, were reelected.

HEREDODEGENERATION OF THE MACULA LUTEA

A Study of the Clinical and Pathologic Aspects

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SOUTH BEND, IND.

HEREDOMACULAR degeneration is classified [1] as one of the subtypes of primary retinal degeneration because it is said to involve the neuroepithelium (rod-cone layer), known as the primary, or first, neuron layer of the retina. The disease is characterized by involvement of the macula, in a bilateral fashion, having hereditary character but lacking any central nervous system change as part of the ocular disease.

Jonathan Hutchinson made the first contribution to this group in 1875. In 1920, when Behr [2] recognized the familial tendency and indicated the probability that the change in the lesion was due to aging and stress, he subdivided the group into the infantile, juvenile, presenile, and senile types. Since then, many cases have been described, and from these it is concluded that for clinical purposes [3] three rather definite forms exist and the macula assumes a different pattern in each of these types.

Type I. This lesion is characterized by a flat, circinate area which is well delimited, having a reddish color only slightly different from the adjacent retina. Later these areas develop yellowish spots with pigmentary change.

Type II. In this type the lesion is characterized by the early appearance of a round, elevated area which assumes a cystic configuration, the inner surface probably being the internal limiting membrane and the base being formed by a rather homogeneous yellowish mass. The contents of the cyst are clear.

During the adolescent or early adult years, this cystic area acquires a peripheral ring of pigment and then ruptures. Remaining will be a gray-white area, which initially has a soft appearance with pigment clumps interspersed. As the patient grows older, the gray-white area assumes a harder appearance, and throughout this period (until the third or fourth decade) a circle of retinal reflex high lights and yellowish-white accumulations surround the lesion.

As time progresses, the lesion takes on more and more the appearance of complete atrophy of the central retinal architecture, and extensive choroidal sclerosis ensues.

Type III. In this type a rather dissimilar process is initiated by stippling in the form of a salt-and-pepper arrangement, which finally becomes more extensive, with larger accumulations of pigment and white glistening material. The retinal layers atrophy, and sometimes a hole will be seen in the fovea.

An important differentiation in the three types is evident in that the central visual accuity is impaired very early in the process associated with Type I and

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Type III. In Type II the central vision is quite good until rupture of the cyst, which is usually during the second or third decade of life. In Type II the ophthalmoscopic changes are noted earlier during the life of the affected person than in Type I and Type III, and the extent of the macular disturbance is seemingly out of proportion to the small amount of visual disturbance.

HEREDITARY CONSIDERATIONS

The hereditary characteristic is generally believed to be of the dominant variety. This belief is set forth by Vossius,[4] Weisel,[5] Jung,[6] and Franceschetti.[7] Berkley and Bussey [8] state that this disease is "a condition of dominant transfer with imperfect penetrance." Falls,[9] in reviewing the problem, concluded that the inheritance was due to a dominant gene. As will be seen from the present clinical study, the inheritance is of the dominant type.

CLINICAL CONSIDERATIONS

Heredodegeneration of the macula Type II is initiated early in the first decade and progresses throughout life. Since the visual acuity in nearly all the reported cases is good during the early phase, it may be presumed that the first neuron layer is capable of physiologic function, in contrast to the conditions in other primary degenerations involving the central area, in which visual loss is early and frequently out of proportion to the ophthalmoscopic evidence of retinal change. Because of this feature, one might question the merit of classifying this particular type as one of the primary retinal degenerations.

As to the nature of the initial process, all structures posterior to the rod and cone layer may be implicated. Falls [9] postulated the choriocapillaris as the offender, on the basis of the preservation of good visual acuity during the early years of the disease in the affected members whom he studied. The pigment epithelium may be involved either in a process of gliosis or, possibly, in some type of fatty degeneration which initiates the early disorder. As the disease advances the cones of the macula are probably secondarily involved and the visual acuity lessens. In the final stage, the microscopic studies indicate great similarity to the change seen in senile macular degeneration.

CLINICAL STUDY

The pedigree (Fig. 1) of the family upon which this study was based is presented. From the familial evidence it may be concluded that this type of macular heredodegeneration is a dominant hereditary tendency.

The proposita, IV-9, was first seen in 1947, at the age of 5 years. The mother, III-14, of this child volunteered the information that bad vision "ran in the family" and was concerned regarding her offspring. The family was of English-Irish descent, and most of them lived in Ohio and Indiana.

There is no history of nervous or mental disease among any of the members of the family, and the majority are engaged in the farming industry or in household tasks. While no specific testing was done, the members examined seemed to be of normal, or above normal, intellectual capacity.

The following as a summary of the known affected members of the family whom I examined.

I-1: This man, born in 1838, had been deceased for several years, but members of the family who knew him stated that his vision was faulty and that his difficulty was similar to the other members of the family who were affected by this trouble.

II-3: This 85-year-old man stated he had had difficulty with his close work very early in life. No glasses were available, and he had worn none for some time. With a portable Snellen chart his uncorrected visual acuity was 5/200 in the right eye and 5/200 in the left eye. Ophthalmoscopy revealed generalized retinal atrophy in the macular area and extensive choroidal sclerosis. Interspersed among the sclerotic choroidal vessels was an occasional round area, resembling a moderate-sized druse.

III-8: This woman, 60 years of age, stated that her visual troubles began about the age of 13 years. She received her first glasses at the age of 26 and had not been able to read newsprint since about the age of 50. In her right eye with best correction (+ 3.25 sph ⌒ + 1.00 cyl, ax 180) she achieved 16/200 vision and in her left eye with + 2.75 sph ⌒ + 0.75 cyl, ax 165 she achieved 14/200 vision. Ophthalmoscopy revealed the right macular area to have several round, rather hard-appearing white areas, which were joined by a similar whitish material arranged in linear connections, which assumed a stellate configuration. The left macula had a seemingly more advanced process, with retinal atrophy and pigmentary change. The whitish areas were not evident, as in the right eye, nor were the linear formations present. Field determinations were unsatisfactory, owing to poor fixation.

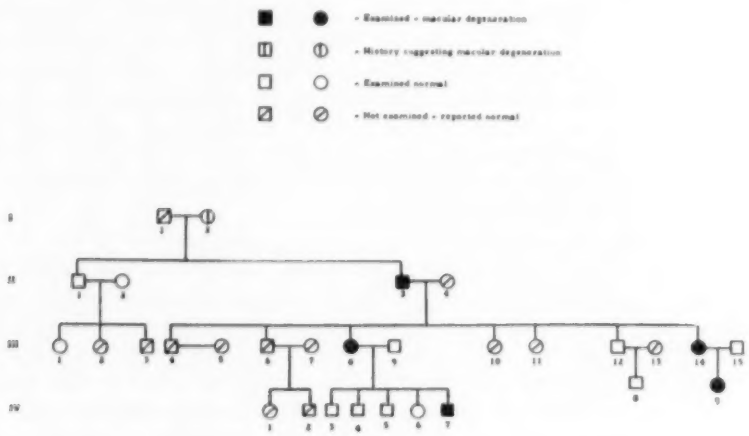
- Examined - macular degeneration
- History suggesting macular degeneration
- Examined normal
- Not examined - reported normal

Figure 1

III-14: This woman, 48 years old, had noted defective vision since the second decade of life. At the time of her first visit she had only slight impairment of red-green color perception (Pseudo-Isochromatic Plates of the American Optical Company), and this was probably due to secondary changes in her central defect. She had a bilateral central scotoma within the 20-degree circle of the Bjerrum screen, using a 3/1000 test object. Her visual acuity with best correction (+ 5.00 sph ⌒ + 2.00 cyl, ax 90) for the right eye and + 6.00 sph ⌒ + 2.00 cyl, ax 90 for the left eye was 20/70. Ophthalmoscopy on the right revealed a complete encirclement of the macular area, the circle being about 2 disc diameters in size and consisting of multiple small yellow-white spots, of varying magnitude. This, I believe, represented the periphery of the original cystic lesion. Within this circle were conglomerate whitish areas which were associated with only slight pigmentary change. In the left eye the remnants of the original lesion were characterized by a lighter retinal coloration than that of the surrounding area, and within the circle were whitish areas associated with more extensive pigmentary change.

IV-7: This 20-year-old man was seen after his separation from the armed forces, where he had completed three years' service. He had a small central scotoma on the right within the 10-degree circle of the Bjerrum screen when a 3/1000 test object was used. There was no evidence of color blindness with the American Optical Company's Pseudo-Isochromatic Plates. His visual acuity with best correction for the right eye of + 3.25 sph ⌒ + 0.25 cyl, ax 180 was 20/40 vision, and with correction for the left eye of + 2.75 sph ⌒ + 0.25 cyl, ax 90 was 20/30.

Ophthalmoscopy on the right revealed the macula to be encircled by an area of depigmentation of about 2½ disc diameters, with a halo of small retinal folds and retinal high lights. This surrounded an area of white proliferative material, which, when viewed with a binocular ophthalmoscope, projected from the retinal surface like a collar button. This area had clumps of pigment on its surface, and the edge had soft yellowish-white accumulations. On the left was a round area, of about 2 disc diameters, which was slightly elevated, in watchglass fashion, and speckled with pigment and white spots.

IV-9: This 5-year-old girl was brought primarily because her mother was concerned lest "she have eyes like some of the other members of the family." The child had 20/20 vision in each eye, and there was no significant refractive error on retinoscopy. She was not color-blind and with the tangent screen had no central defect.

Ophthalmoscopy revealed on the right a cystic formation in the macular area of about 1½ disc diameters, which had a yellow, homogeneous base. With the binocular ophthalmoscope the surface of the cyst extended above the retinal plane. This cyst was fixed and did not move with ocular motion; its contents were clear and were surrounded by a ring of pigment. The left eye was of similar appearance.

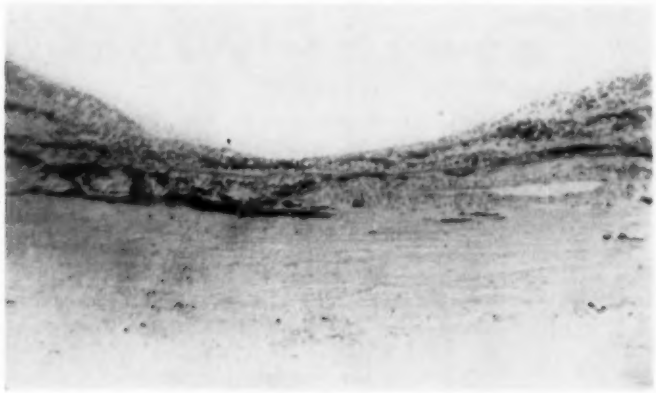

Fig. 2.—Degeneration of macula.

PATHOLOGIC FINDINGS

No one has obtained an eye for histopathologic examination during the early phase of this disease. I was fortunate in obtaining the eye of II-3, who died at the age of 87. This eye was submitted to Dr. Bertha Klien, of Chicago, for study and diagnosis, and herewith I include her report (Fig. 2).

The anterior segment is normal, the ciliary muscle is of the hyperopic type, the ciliary processes show senile hyalinization. The main pathologic changes are found in the macular retina. There is an extensive defect of the first neuron, its nuclei are absent over an area of 2 disc diameters temporal to the nerve head. The pigment epithelium is missing over a less extensive area. In the foveal and adjacent region a glial membrane replaces the pigment and neuroepithelium. The pigment epithelium is present for about ½ DD temporal to the disc but its cells are flat and irregular. They appear of similar shape on the other side of the macular defect before they assume normal appearance again. Bruch's membrane is very obvious due to a bluish cast, which is deepest at the posterior polar region and becomes uneven toward the periphery. In the circumpapillary and macular zones there are numerous breaks in it. V. Kossa stain was faintly positive, indicating some calcification of Bruch's membrane. The choriocapillaris is completely absent in the posterior polar region and here the large choroidal vessels show marked sclerosis of the senile involutionary type, viz., thickening of the media and adventitia but no hyalinization. In the macula there are several bleb-like spaces between external limiting and Bruch's membrane which contains finely granular debris of a bluish color (calcium?). There is a partial atrophy of the temporal half of the optic nerve with some glial proliferation.

The marked choroidal sclerosis, fragility and calcification of Bruch's membrane and the atrophy of the choriocapillaris are senile changes and are coexisting with the primary macular retinal degeneration.

Diagnosis.—Heredodegeneration of the macula lutea, infantile type, at age of 87.

SUMMARY AND CONCLUSIONS

This report describes a family from Ohio and Indiana affected by heredodegeneration of the macula lutea Type II. The disease is characterized by a dominant genetic trait, and the affection appears to have particular affinity for the region of the macula, which undergoes a gradual process of degeneration.

As is indicated, the macular change associated with Type II is set apart from the other primary retinal degenerations by the preservation of central visual acuity and color perception until secondary changes ensues. For this reason, classification of this disease as one involving the rod and cone layer of the retina would seem to be incorrect.

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Dr. Bertha Klien, Chicago, cooperated in the preparation of this paper.

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NERVE CHANGES IN THE HUMAN CORNEAL GRAFT

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SEVERAL investigators * have observed regressive nerve changes of the Wallerian type, followed by progressive changes, after experimental keratotomies and keratoplasties. It is true that one has more material for the histologic demonstration of what happens with the corneal nerves in experimental keratoplasty, but when one tests the rabbit for return of sensitivity, one can obtain little information of value. The experimental grafting can be suitably timed to study the condition of the nerves of the graft at different periods after the operation, an investigation which is of value.

With human keratoplasty, on the other hand, morphologic studies are limited to those cases in which there is eventual need of repeating the operation, and this is done at a time, not when it is desirable for the study of the nerves, but when it is convenient and necessary for the patient. Most retransplants are made several months after the first operation, and nothing can be observed of degenerative nerve changes. One has to be content with demonstrating the presence of new nerve fibers in the graft. On the other hand, in human transplants one gets better information regarding the return of sensitivity, quantitatively and qualitatively. In the rabbit one has to be satisfied with obtaining a corneopalpebral reflex as the only means of proving return of sensibility, since lower degrees of sensibility during the early days cannot be detected by subjective means. On the contrary, in the human graft one can obtain information of the status of corneal sensitivity before one can provoke a palpebral response.

Very few observations have been reported on the nerve changes that take place in the human corneal graft. In 1946, Babel and Campos [11] studied the regeneration of nerves in four human corneal grafts and found that vascularization preceded and conditioned the reinnervation of the grafts. These grafts were all opaque and were performed in leucomatous corneas. The authors did not find a subepithelial plexus and concluded that the number of nerves present was not sufficient to keep the graft clear. Of the four grafts, one was 36 days old and showed no nerves; another was 44 days and nerves were already present; the other two were over 10 months and were reinnervated.

In 1947, Franceschetti and Babel [12] had the opportunity of examining sections of a clear graft that was obtained from a patient who died six years after operation. They found a subepithelial plexus and no nerves in the stroma. Where capillaries penetrated the graft they were followed by fine nerves. The authors concluded that the reinnervation of the graft was secondary to its vascularization, that a vessel-less graft has no nerves, and that the presence of the subepithelial plexus conditions its transparency.

The present study is based on two kinds of observations: (*a*) those gathered from the clinical follow-up and analysis of patients with corneal transplants, either clear or opaque, and (*b*) histologic study of human grafts obtained from cases of retransplanting. Most of these patients suffered from keratoconus and were operated on by Castroviejo and me, following his technique of square, partial penetrating keratoplasty.

A. CLINICAL TESTING OF GRAFTS

Clinical testing was carried out in 50 grafts, most of them in individual patients, some of whom had had operations on both eyes.

Since I have found experimentally that the first responses to stimulation of the graft were not obtained until 40 to 50 days after operation, I started testing about the 40th day. There is an advantage in working on an eye that has already quieted down,

* References 1 to 10

in that one eliminates a misleading response due to fear or excitement of the patient and also avoids the introduction of an extra irritating factor and the increased risk of complications. Patients who had had grafting performed in previous years and who came for a check-up were subjected to the test. Thus I had the opportunity of seeing some patients who had been operated on several years before—some up to 10 years previously.

Of these grafts, 34 were clear, 2 translucent, 4 cloudy, and 10 opaque. In only six had there been central anterior adhesion to the edge of the graft and need of a secondary operation. Most of the patients were white persons from 18 to 30 years of age.

The testing was performed with a cotton brush. A small piece of cotton was rolled between the thumb and the index finger, leaving its end fluffy, so as to make a fine brush 2 mm. in diameter. It

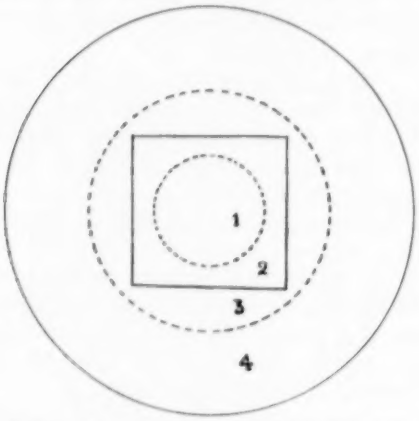


Fig. 1.—Division of cornea into four zones: (*1*) center of graft, (*2*) periphery of graft, (*3*) host cornea surrounding the graft, and (*4*) perihpery of host cornea.

was found that when corneal sensitivity was decreased, a needle point did not give satisfactory results, and it was necessary to stimulate a larger area to obtain adequate information.

The cornea to be tested was divided into four zones: (1) the center of the graft; (2) the periphery of the graft; (3) the host cornea surrounding the graft, and (4) the periphery of the host cornea (Fig. 1). This division is not an arbitrary one but is based on the fact that experimentally I found anesthesia not only in the graft but also in the host cornea surrounding it and that the same areas showed Wallerian degeneration of their nerves.

When testing, care was exerted not to touch the lashes with the brush and the contact was as gentle as possible. The entire cornea of the eye operated on and that of the fellow eye were subjected to the test to establish a comparison between them. The test was explained to the patient so as to obtain his cooperation without apprehension. He was asked to report any sensation felt and to differentiate its intensity. To acquaint him with the test, I always tested the fellow eye first.

In the 40-day grafts it was found that in some of them there was sensitivity in the host cornea surrounding the graft, in the cicatrix at the junction, and in the extreme periphery of the graft. Other patients did not feel the cotton brush in the graft or on the cicatrix but felt it in the host cornea surrounding it, although with less intensity than in the periphery of the host cornea. When sensation was present in the cicatrix and in the periphery of the graft, it was rather dull, and not strong enough to provoke a blinking reflex. It was interesting to find that the clear and the opaque grafts responded alike.

From the 40th up to the 90th day the sensitivity in the host cornea, in the cicatrix, and in the periphery of the graft increased in intensity, and a palpebral reflex began to appear. At the same time the sensitive area increased toward the center of the graft.

Up to the sixth month the sensitivity increased. The patients continued to feel the stimulus better, although still less than in the host cornea. Some showed an irregular pattern of the sensitive area. An interesting fact was that its progress toward the center of the graft was very slow. The palpebral reflex was obtained when the periphery of the graft was stimulated. Between the 6th and the 12th month there was little change, except for the patient's indication that the stimulus was felt better and a palpebral reflex was more frequently obtained from the graft. At the end of the first year a dull sensitivity was still present in the center of the grafts.

During the second year the sensitivity increased in the whole graft. In its periphery it had reached the same threshold as in the host cornea, but in the center it was dull, even at the end of the second year. A palpebral reflex was obtained from the periphery, but not from the center.

In the following years the center of the graft gained sensitivity and a palpebral reflex was obtained. The cases of 7 and 10 years'

duration showed sensitivity in all the grafts, of the same quality and quantity as in the host.

As a rule the progress of sensitivity was centripetal in relation to the graft and the same around the entire periphery. Nevertheless, irregular patterns were observed; some showed the sensitivity more advanced in one angle of the graft or in its upper or lower half.

Thirty-seven of the cases analyzed were of keratoconus in an advanced stage, and 13 of corneal leucomas, dystrophies, or decemetoceles. In all the cases of keratoconus the return of sensitivity followed the pattern described. In the cases of corneal leucomas some variations were observed; some cases followed the normal recovery, but others showed a delay in the process of return of sensitivity. One patient of this group, in spite of having a clear graft, showed no sensitivity after several years. One patient with decemetocele had a normal course. One patient with a dry epithelial dystrophy was insensitive after five months; the graft was clear, and the host cornea showed a dull response.

In comparing what happened in the clear and in the opaque grafts, it was apparent that in the clear graft return of sensitivity started about the 45th day at the periphery, increased in intensity, and progressed toward the center very slowly, and that after the 20th month there was response in the whole graft, although dull in the center. Among these clear grafts there was one, performed in a corneal leucoma, in which no response was obtained after several years.

In the opaque grafts it was apparent that the return of sensitivity took place about the same time as in the clear graft, but it progressed faster toward the center, so that in the graft of one year the stimulus was felt already in the center of the graft. All these opaque grafts were vascularized, and the blood vessels, creating a pathway of less mechanical resistance, facilitated the penetration of the new axons in the graft. Other authors and I have demonstrated histologically that some nerves follow the blood vessels.

Whenever a decreased sensitvity in the host cornea and marked delay in the reinnervation of the graft existed, it was due most likely to the nerves of the host being altered by the original pathologic process.

In studying the grafts with the biomicroscope, it was possible to observe the corneal nerves in a clear graft of nine years. These appeared as thin whitish threads with dichotomous division and of normal thickness. The sensitivity here was normal, and there were no blood vessels.

B. HISTOLOGIC STUDY OF GRAFTS OBTAINED FROM CASES OF RETRANSPLANTATION

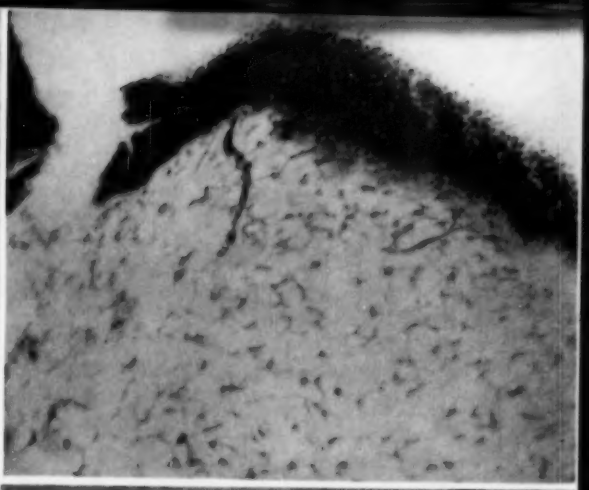
For this work we studied 20 grafts, 19 of which were opaque and 1 clear. All the graftings were performed in advanced cases of keratoconus; all the grafts became opaque, and the patient underwent a second operation from eight months to several years after the first one. All these grafts, beside being opaque, were vascularized.

The grafts obtained were carried through the Gros-Schultz method for the staining of nerve axons, by which the axis cylinders are stained black.

For the sake of brevity, only five cases are detailed; four of opaque and one of a clear graft. All the opaque grafts showed the presence of nerves.

REPORT OF CASES

CASE 1.—A 29-year-old woman with advanced keratoconus. A square, partial penetrating keratoplasty was carried out in her right eye. The graft remained clear for four weeks, when it became opaque and moderately vascularized. On testing the graft for sensibility, it was found that there was normal sensitivity in the cicatrix and in the periphery of the graft and low sensitivity in the center. A second keratoplasty was performed on the 10th month and the graft removed studied for nerves. In the stroma there were many normal-looking nerves (Fig. 2), formed by several nerve fibers or a single one. The axons were of variable caliber, some fine and others thick. In the same trunk there were axons of different sizes. In most of the nerves a sheath of Schwann was not apparent; they seemed naked, indicating an incomplete reinnervation. However, some nerves were already sheathed, most likely from an old sheath that had been penetrated by the regenerating axons. I have also found that the epi-



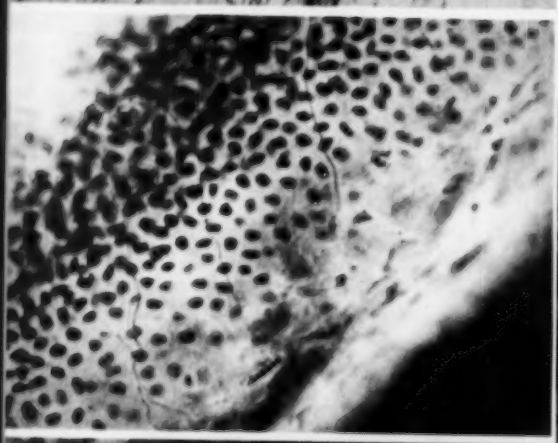


Fig. 2.—Regenerated nerves in the stroma of an opaque graft of 10 months.

Fig. 3.—Nerves in the epithelium of an opaque graft of 10 months.

Fig. 4.—Normal-looking new nerves in an opaque graft of one year.

Fig. 5.—Regenerated nerve trunks in an opaque graft of 10 months.

Fig. 6.—Subepithelial nerves in an opaque graft of 10 months.

Fig. 7.—Opaque graft of one year with new regenerated nerves.

Fig. 8.—New neurites in the subepithelium of an opaque graft of one year.

(Figures are arranged in order from upper left to lower right.)

thelium is equally invaded by the new elements (Fig. 3); there were single naked axons with beading, not always very apparent, among the epithelial cells.

Opaque graft of 10 months in a case of keratoconus. Before the second operation, the graft was opaque and vascularized, and there was return of sensitivity, although dull in the center. The sections show the presence of new nerves in the stroma, as well as in the epithelium.

Case 2.—A 20-year-old youth with advanced keratoconus in the left eye. A square, partial penetrating keratoplasty was performed. The graft remained clear for a month, at the end of which an inflammatory reaction set in and the graft became rapidly opaque and vascularized. One year later the eye was quiet and the graft opaque and moderately vascularized; no synechia was present. The testing of the graft for sensitivity elicited normal sensibility in the periphery of the graft and a decreased one in the center. A palpebral reflex was obtained on stimulating the cornea. A second keratoplasty was then performed. The sections of the first graft showed a moderate amount of new nerves in the stroma. Besides thick trunks formed by a variable number of axons of different caliber, there were many single axons. Not all the new nerves were contained in a sheath; however, the majority were (Fig. 4). Most of the new axons were thin. It is apparent that there are not always blood vessels in the vicinity of the new nerves. In the epithelium there were fine, single-axoned nerves.

Opaque graft of one year in a case of advanced keratoconus. There was return of sensibility in the whole graft and moderate vascularization. Normal-looking new nerves are observed in the sections and do not always follow a route along the blood vessels.

Case 3.—A 42-year-old woman with advanced keratoconus. A large square, partial penetrating keratoplasty was carried out. The graft remained clear for a month, at the end of which the eye became red, painful, and photophobic, and the graft clouded rapidly. Ten months after the operation the graft was opaque, with some blood vessels in the stroma. On testing the cornea, sensitivity was elic-

Fig. 9.—Clear, vessel-less corneal graft of nine years, with normal nerves in the stroma.

Fig. 10.—Nerves in the stroma of a clear graft of nine years.

Fig. 11.—Nerves in the epithelium of a clear graft of nine years.

Fig. 12.—Subepithelial nerves in a clear graft of nine years.

(Figures are arranged in order from top to bottom.)

ited in the periphery of the graft, and to a less degree in its center. In general, sensitivity was rather dull, and a palpebral reflex was not obtained. There was no synechia. A second corneal graft was performed on the 10th month. The examination of the sections revealed the presence of new nerves in the stroma in moderate number. Besides single axons, there were trunks with several axons of different caliber (Fig. 5). Some were naked axons, but most of them were provided with a sheath. There were still rare degenerated nerves. Blood vessels were present in the stroma, and, though it is true that some nerves followed them, most of the new elements did not accompany the vessels. Subepithelial nerves were also observed (Fig. 6).

Opaque graft of 10 months in a case of advanced keratoconus. Sensitivity was detected in the whole graft, of a quality inferior to that in the host cornea; the center of the graft showed a duller response. The regenerated nerves do not always follow the blood vessels.

CASE 4.—A 15-year-old youth with advanced keratoconus in both eyes. A 6 mm. square, partial penetrating graft was performed in the left eye. On the fourth week an inflammatory process set up in the eye, and the graft, so far clear, became rapidly opaque and moderately vascularized. The graft remained unchanged for a year, when it was opaque, with some blood vessels in the stroma. There were no synechiae. There was return of sensibility in the whole graft, duller at the center. No palpebral reflex could be elicited. One year after the first operation a second keratoplasty was performed. The graft removed was carried through the routine process of silver impregnation, and on examination many normal-looking new nerves were seen in the stroma. They were formed of several axons of different caliber (Fig. 7). Each axon had a uniform diameter. They were naked or lay within a sheath with some Schwann nuclei. Axons were also observed in the epithelium and subepithelium (Fig. 8). The new nerves did not always accompany the blood vessels when invading the graft.

Opaque graft of one year in a case of advanced keratoconus. The graft was found to be sensitive and contained many new nerves in the stroma, as well as in the epithelium. The blood vessels were not always followed by the regenerated nerves.

CASE 5.—A 28-year-old man, who in 1938 had had a keratoplasty in both eyes for advanced keratoconus. The transplants remained clear, but there developed marked irregular astigmatism, to correct which a second keratoplasty was performed in the left eye in 1942 and in the right eye in 1947. Before the last operation in the right eye, the transplant appeared clear, and examination with the slit lamp showed several well-developed nerves in the stroma. No blood vessels were observed in either the graft or the host. On testing the cornea, a normal sensibility was found in the graft and a brisk palpebral reflex was elicited.

The study of the removed graft revealed a normal innervation (Figs. 9 and 10). The nerves were of normal appearance and were formed by a variable number of neurites of different caliber. Except for some rare naked axons, all were provided with a Schwann sheath with few normal nuclei. There were no empty sheaths. The new nerves were present in the subepithelium, as well as in the epithelium (Figs. 11 and 12). The epithelial nerves were single-axoned and very fine. No blood vessels were found.

Clear graft of nine years with full sensibility and nerves looking normal to the slit lamp and histologically. Nerves are found in the stroma, as well as in the subepithelium and epithelium. There are no blood vessels.

SUMMARY AND COMMENTS

Experimentally, in a previous paper, and now clinically and histologically in the human corneal graft, I have demonstrated that reinnervation of the graft takes place no matter whether it remains clear or becomes opaque. In the human graft, response to the stimulus is obtained about the 45th day after the operation, first at the periphery of the graft, and gradually spreading toward the center until a response is obtained here also. At the onset the response indicates a hyposensitivity, and no palpebral reflex is obtained. As time goes on, the sensitivity increases and a palpebral reflex is elicited about the 12th month, which is more constant after the second year. In the graft of several years' duration the sensitivity is normal in the whole cornea. I have shown experimentally that the beginning sensitivity is the result of the invasion of the graft by new neurites, which have sprouted from the nerves of the surrounding host cornea. The cases here reported of grafts of 10 and 12 months' duration, opaque and vascularized to a variable degree, show a return of sensitivity in the whole cornea, to a less degree, however, at the center. The sections of these grafts permit the demonstration of the

presence of new nerves of a normal appearance, which are present not only in the corneal stroma, but in the epithelium as well. The new nerves do not always follow the path of the blood vessels. Some nerves are naked, but most are provided with a sheath of Schwann. The reinnervation of the graft follows a more normal pattern in the cases of keratoconus. In leucomas and corneal dystrophies the process is somewhat delayed. In comparing the clear and the opaque graft, it was observed that restoration of sensitivity started about the same time; however, it progressed faster in the opaque vascularized graft. The fact that the clear graft, avascular as it is, is reinnervated in the same way as the opaque one proves that vascularization of the graft is not a requirement for its reinnervation. The new nerves invade the graft in spite of the absence of blood vessels; nevertheless, their presence facilitates it, allowing the new nerves to follow a pathway of less mechanical resistance.

The importance attributed to the nerves in the final outcome of corneal grafting is exaggerated. There is no doubt that the presence of nerves plays an important role in its trophic and nutritional balance, but has very little or nothing to do with its transparency or opacification. The clinical response obtained, and the presence of nerves in the sections of clear and opaque grafts, are eloquent proof of how little the presence of nerves has to do with successful keratoplasty.

Dr. Ramón Castroviejo furnished the clinical material used in the preparation of this paper.

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LYMPHOMATOUS TUMORS OF THE EYE

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TWELVE years ago, in 1942, I presented before this Section on Ophthalmology a study of 21 patients with lymphomatous tumors involving the eye from the Institute of Ophthalmology of Presbyterian Hospital, New York, and the Memorial Hospital for Cancer and Allied Diseases. Each of these tumors had been verified by biopsy and the patient had been followed for a period of four years. Four patients had had generalized disease before the ocular tumor was found; in 17 the tumor was thought to be primary in the region of the eye. However, it was later determined that 2 of these 17 patients had practically simultaneous onset of ocular and generalized lymphomatous disease. At that time, 5 of the 21 patients had died, 5 were alive with tumor, and 11 were alive without evidence of tumor, either local or general.

Particular interest was paid to a group of patients with subconjunctival lymphomas which had the same clinical appearance irrespective of the histologic type or clinical course.

The problem of classifying tumors made up of small cells of the lymphocytic series was discussed, but not settled. It was concluded that patients with lymphoma would have to be followed longer than four years before any conclusions could be drawn about the behavior of certain types of these tumors.

At that time this group of ocular lymphomas was the largest on record. Since then larger series have been published, but the follow-up periods have been so short and so indefinite that few conclusions could be drawn.

It has been my good fortune to be able to trace 20 of the 21 original patients and to determine their status as of early 1954. I have not attempted to add any patients for whom subsequent diagnoses have been made, either in New York or in Philadelphia, in order that the first follow-up, of four years, and the second, of 15 years, might be made easily comparable.

This group is so small that each patient makes a difference of 5% in the statistics. However, it is the only group of cases of ocular lymphomas that has been completely verified by biopsy and the patients followed for a suitable length of time.

INCIDENCE

I can find only two reports of larger groups of ocular lymphomas. Heath covered 67 tumors but was not concerned with survival rates. Of these 67 tumors, 30 involved the conjunctiva. The duration was known for only 19, and the follow-up of these averaged only 2.12 years. Not all his patients had biopsies of the orbital lesions. Reese's book on "Tumors of the Eye" [20] lists 61 cases of ocular lymphomas. This figure includes the 21 cases which I have followed. The fate of those cases collected since 1942 at the Institute of Ophthalmology has not yet been determined.

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Heath's [2] cases of ocular lymphoma represented 4% of all the lymphoma cases from an active lymphoma clinic in Boston. Another recent survey, this one made at the Massachusetts General Hospital, showed that 1.7% of the lymphoma clinic patients were classified as presenting lymphomas in the ocular adnexa. Sugarbaker and Craver [3] had reported that 1% of the extranodal primary lesions were in the eyelid and orbit. Of their patients with generalized lymphosarcomatosis, 1.5% had secondary involvement of the eye.

Schulz and Heath [4] reported that less than 1% of a total of 1,671 ocular tumors were lymphomas primary in the region of the eye. My findings,[1] based on the Institute of Ophthalmology pathology collection in 1942, showed that 1.76% of extrabulbar tumors were primary lymphomas and 2.65% were primary and secondary lymphomas. Rones * found only 19 lymphomas in 11,500 ocular specimens of all types of diseases (not tumors alone) at the Armed Forces Institute of Pathology up to 1942, an incidence of 0.025%.

Generalized lymphomatous diseases, including Hodgkin's disease and leukemia, are rather common, as evidenced by Craver's [5] report of 5,000 deaths from malignant tumors in New York City in a six-year period, 1 tumor out of every 16 being lymphomatous.

TABLE 1.—*Incidence of Subconjunctival Lymphomas*

		Follow-Up	
		No.	Period
Heath	1.8% of all tumors originating in ocular adnexa	19	2.12 yr.
Rones (AFIP)	0.025% of all ocular specimens of all diseases	None	
McGavic	0.736% of all extraocular tumors	6	14 yr. (Minimum)

No report in literature shows leukemia associated with this type of lymphoma.
All report these tumors as "least malignant."
Clinical appearance was the same for patients who died as for those who lived. Histologic appearance was also unsatisfactory for prognostic purposes.

Thus, one sees that the reported incidence is quite variable, depending upon the manner of selection of material, especially whether or not a biopsy of the ocular lesion is made, whether tumors are carefully screened as primary or secondary, and what site the ocular tumor involves (e. g., orbit *vs.* conjunctiva).

CAUSE

The cause of the lymphomas is not known. Most of them appear to be purely neoplastic. However, as one watches the development and course of lymphomas, one cannot help feeling that some of them are initiated by inflammatory processes. Braley and Alexander [6] reported the isolation of a virus from a patient with bilateral orbital lymphoma. One of the patients in the series I reported in 1942 had had granulomatous pseudotumor of first one orbit and then the other. The dermatologists recognize a condition known as mycosis fungoides which may develop into lymphosarcoma.[7] This is in addition to the usual lymphosarcomas of the skin, which are the same as those developing in any nonlymphoid tissue of the body. Animal experiments continue to indicate more than a slight relationship between virus diseases and lymphomas. It is for this reason that the term lymphomatoid diseases seems a more accurate and descriptive one than lymphomatous tumors.

* Rones, B., in discussion on McGavic.[1]

CLASSIFICATION

The lymphomatoid diseases are poorly understood, difficult to classify, and abounding in peculiar variations. The separation of one type of lymphoma from another can be made only for a given time, because one type may change into another, and leukemia may develop along with any of the usual types of malignant lymphoma.

Transition from follicular lymphoma to reticulum cell lymphosarcoma or to Hodgkin's disease, with or without lymphocytic leukemia, is a good example. Custer [8] has stated that "malignant lymphoma appears to be a single neoplastic process having a multiplicity of histologic patterns. The pattern may be a static one throughout the course of the disease, but it is frequently a changing one, and two or more patterns may exist in the same patient, even in the same tumor mass."

This interrelationship is borne out several times in the cases here presented. Confirmation of this has also been made by Warren and Picena,[9] Gall and Mallory,[10] Craver,† and others.

We therefore must think of the lymphomatoid diseases as having probably both monocentric and multicentric origins. We must expect them to change from one form to another, to develop leukemia in certain instances, and to show variations in response to x-ray therapy. Repeated biopsies, blood counts, and bone marrow studies are necessary to demonstrate the changes occurring in the course of the patient's disease.

SURVIVAL

The popular impression among physicians is that once a patient has any form of lymphomatoid disease, he is certain to die of disseminated lymphosarcomatosis. While it would be difficult, if not impossible, to prove that anyone has been cured of lymphosarcoma, the literature reflects a more optimistic attitude now than it did 15 years ago. This is not because of the introduction of any new form of treatment. It is, rather, a difference in philosophical approach and in the better application of standard methods of treatment.

When a patient presents himself with evidence of Hodgkin's disease, reticulum cell lymphosarcoma, or leukemia, it is almost certain that he will die, despite all treatment. However, if he presents himself with a localized lymphocytic cell or giant follicle lymphosarcoma, it is necessary that the physician proceed on the working basis that the patient has a local lesion only and that eradication of this tumor will result in cure. Sometimes the generalized disease is demonstrated a short time later. Sometimes the patient dies of a completely unrelated condition. This may not occur until his normal life expectancy has been passed. This does not mean that any of these diseases is considered "curable" in the usual sense; but if a patient can be made to live comfortably until he is 70 or 75, without demonstrable evidence of disease, it would seem to me that a desirable therapeutic result had been achieved.

In a group of diseases varying as widely in general characteristics as do the lymphomatoid diseases, it is particularly appropriate that we speak in terms of 5-, 10-, and 15-year survivals, rather than in terms of cures. Before showing the survival rates for my relatively small group of ocular lymphomas, I should like to summarize briefly the general survival rates for the same diseases occurring elsewhere in the body.

† Reference 5. Craver, L. F., in Pack and Livingston.[11]

Craver [5] (Table 2) reported in 1947 an improvement in the five-year survival figures as compared with a report made in 1940: Hodgkin's disease, 20% five-year survivals; lymphosarcoma, 26%; lymphatic leukemia, 15%, and myelogenous leukemia 5%.

Stout,[12] in 1942, using a different classification for lymphosarcoma, reported a five-year survival rate of 16.5%. He extended the follow-up period to 10 years and found that 9% of all the patients were alive, with or without tumor. He stressed the variation in survival rates according to the histologic types of lymphosarcoma, thus: reticulum cell, 8%; lymphocytic cell, 12%, and giant follicle, 24%. He believes that the disease usually has a focal origin. He also made the interesting observation that 2 to 3% of all patients have a long survival irrespective of the degree of involvement or of the treatment given.

Gall and Mallory [10] reported a 5-year survival rate of 22% and a 10-year survival rate of only 4%. They found that leukemia occurred in about 10% of their cases, while Stout [12] found it in 2.3% and Sugarbaker and Craver [3] in 6.6%.

TABLE 2.—*Over-All Survival Rates of Lymphosarcoma in Two Series from Literature*

	Five-Year	Ten-Year
Stout [21] (1947)	23%	13%
Craver [5] (1947) *	20%	....

* One-half of survivors had first involvement in head and neck.

TABLE 3.—*Survival Rates for Fifty Patients* with Lymphosarcomas of Head and Neck*

Survived 5 yr.		52%
Primary at first examination	46%	
Survived 5 yr.	61%	
Additional involvement of cervical nodes at first	54%	
Survived 5 yr.	44%	
Disease became generalized	40%	
Survived	1 patient	

* Catlin,[16] 1948.

Gall and Mallory also found in 10% of their cases localized lesions that would have permitted complete surgical excision, there being no evidence of disease elsewhere in the body at autopsy. In another paper, Gall [13] reported 48 cases of all types with sufficient localization to permit surgical excision. The average postoperative survival was five years.

Hare, Mulry, and Sornberger,[14] in 1948, reported that 29% of their patients were living and well at the end of five years. Their idea was to treat the patient with an obliterating dose of x-rays while the disease was localized.

Helwig,[15] reporting a five-year survival rate of less than 5% in lymphoblastoma and of 50% in follicular lymphoma, felt that the degree of differentiation was more important than the method of treatment, anatomic distribution, or leukemic blood findings.

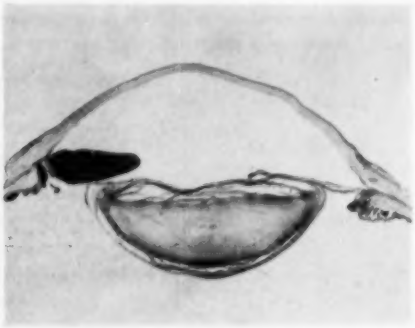
Catlin [16] (Table 3) reported 50 patients with lymphosarcoma of the head and neck, with a five-year survival rate of 52%. Those with primary tumors at the time of the first examination had a 61% five-year survival rate, while only 44% survived if the cervical nodes were involved in addition to the primary tumor. Of the 40% whose disease became generalized, only one patient survived for five years.

Schulz and Heath,[4] in 1948, reported 14 patients with conjunctival lymphomas. These authors felt that the cell type had no bearing on the prognosis. Their follow-up was very short. Their conclusions are at variance with the general literature on lymphomas elsewhere in the body and with the findings in the group presented here.

TREATMENT

Treatment of the lymphomatoid diseases obviously leaves much to be desired, or we would speak in terms of cure rather than of palliation and survival rates. X-ray therapy continues to be the treatment of choice in most cases. Early localized tumors offer the best target both for x-rays and for complete surgical excision.

X-ray therapy may be applied with low-voltage apparatus for superficial lesions and with higher voltage for more deeply placed tumors. The field may be well localized, or the radiation may be given through large portals. The entire body can be irradiated, after the Heublein method.



Lymphoma of iris.

The more generalized forms of disease, especially leukemia, were treated with arsenic until about 1938, when radioactive isotopes (P^{32}) were first given clinical trial.

The nitrogen mustards (HN2 and HN3) came later, as a by-product of war gases. Their effects are similar to those of x-rays. These agents should have special appeal to the ophthalmologists, since with their use damage to the eye, which can be devastating with roentgen radiation, is avoided. These chemical agents have a somewhat selective effect on rapidly growing tissues in the body. They have a particularly destructive action on lymphoid tissue and bone marrow. The danger of their use is in the pronounced suppression of the normal activities of bone marrow. The nitrogen mustards have not been effective in treatment of localized lesions, in which x-rays are most useful. Craver [5] regards the nitrogen mustards as of little use in myeloid leukemia and no value in the acute leukemias or in any of the more aggressive forms of lymphosarcoma. They are used in Hodgkin's disease.

The radioactive isotopes are said to be useful in polycythaemia vera and in chronic myelogenous or lymphocytic leukemia. P^{32} has not shown promise in treatment of lymphosarcoma, Hodgkin's disease, or the acute leukemias. It is perhaps best to say that the nitrogen mustards and the radioisotopes are useful adjuncts to be used with x-ray therapy.

Triethylene melamine has been used by Rottino [17] in the treatment of Hodgkin's disease (47 cases), leukemias (16 cases), and lymphosarcoma (8 cases), with no cures. The best response was in lymphatic leukemia. This drug is also toxic to the bone marrow.

Cortisone is also being used because of its ability to suppress lymphoid tissue.

While one is inclined to think of lymphosarcoma as the prime responder to x-rays, some patients seem to harbor tumors which are relatively resistant. Although the literature contains statements that x-ray therapy does not prolong the life of the patient in the long run, the more carefully controlled series give adequate proof that it does prolong life to some extent, and it provides great comfort to the patient with large tumor masses in certain regions. The more accessible lesions, particularly those in the head and neck, are associated with a better survival rate than those occurring elsewhere in the body.

REPORT OF CASES

In the first report [1] 21 patients were listed. One of these has been lost to follow-up. This patient was a 50-year-old woman who had had a radical mastec-

TABLE 4.—*Intraocular Lymphomata Reported in Literature*

Author	Origin	Year
Wiener	Mediastinum	1902
Hartshorne *	Choroid (?)	1922
Elschnig	Ovary	1926
Kukan	Generalized	1935
Bietti	Generalized	1933
McGavic	Iris	1942
Cooper and Riker	Eye (?)	1950
Reese	Uveal + generalized (3)	1951

* Biopsy of orbit; tumor thought to have ruptured through sclera.

tomy in 1934. In 1936 one eye was enucleated because of a tumor of the iris, which was thought to be a metastatic carcinoma; however, the tumor proved to be a lymphoma, and the patient was alive and well six years after enucleation. She is believed to have died about 1950, but this information is not definite.

This case was the first proved instance of an isolated intraocular lymphoma. Hartshorne [18] had reported a lymphoscarcoma of the orbit, which he thought had originated in the choroid and ruptured through the sclera. Cooper and Riker,[19] in 1951, reported a malignant lymphoma which apparently started within the eye, being first manifested as iridocyclitis. The patient died of generalized reticulum cell sarcoma. There was a history of inguinal lymph node enlargement three years before the eye became involved. In Reese's book [20] there are reports of three additional cases involving the uveal tract; all three patients had generalized reticulum cell lymphosarcoma, and two died in less than one year.

Table 4 shows all the intraocular cases in the literature except for the leukemia cases and two unreported cases in Heath's collection, one of which was of leukemia.

Table 5 shows a summary of the 21 cases.

Table 6 shows the classification of tumors according to histologic type.

Table 7 shows the histologic types of lymphomatous tumors as reported by Reese.[20] This includes the 21 patients in the present series.

TABLE 5.—*Summary of the Twenty-One Cases Reported in 1942*

Age	Sex	Diagnosis	Site	Onset of Ocular Lesion	Onset of Other Lesions	Patient Dead or Alive, April, 1942	Patient Alive with Tumor	Hemogram
60	M	Lymphocytic cell lymphosarcoma	Lids, both eyes	1932	1935	Died, 1936		Leukemia
62	M	Lymphocytic cell lymphosarcoma	Lacrimal gland	April, 1941	None	Alive		Normal
55	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1924 (History)	None	Alive		Normal
56	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1938	None	Alive		Normal
45	F	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, left eye	1940	None	Alive		Normal
52	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1939	None	Alive		Normal
59	F	Lymphoma or lymphocytic cell lymphosarcoma	Lid	1937	None	Alive		Normal
61	F	Lymphoma or lymphocytic cell lymphosarcoma	Left orbit	1940	1941	Alive	+	Normal
50	F	Lymphoma or lymphocytic cell lymphosarcoma	Iris	1936	None	Alive		Not available
47	M	Reticulum cell lymphosarcoma	Lacrimal gland	1941	1941	Alive	+	Not available
53	F	Reticulum cell lymphosarcoma	Lid	1939	None	Alive		Not available
70	F	Reticulum cell lymphosarcoma	Lid and orbit	1937	1939	Died, 1940		Not available
64	M	Reticulum cell lymphosarcoma	Lacrimal gland	1934	1927	Died, 1935		Not available
50	M	Reticulum cell lymphosarcoma	Orbit	1937	1937	Died, 1938		Not available
59	F	Reticulum cell lymphosarcoma	Lacrimal gland	1939	None	Alive		Not available
60	F	Reticulum cell lymphosarcoma	Orbit, both eyes	1931	1933	Alive	+	Not available
54	M	Lymphosarcoma (unclassified)	Subconjunctiva	1940	1940	Alive	+	Normal
52	F	Giant follicular lymphosarcoma	Lacrimal gland	1940	1940	Alive	+	Leukemia
59	F	Lymphoma or giant follicular lymphosarcoma	Lacrimal gland	1937	None	Alive		Normal
68	M	Lymphoma or giant follicular lymphosarcoma	Lacrimal gland	1937	None	Alive		Normal
29	M	Hodgkin's disease	Brow	1939	1934	Died, 1936		Normal

TABLE 6.—*Classification as to Histologic Type of the Tumors in the Twenty-One Cases (1942)*

	No.
Lymphocytic cell lymphosarcoma *	2
(?) Simple lymphoma or lymphocytic cell lymphosarcoma	6
Giant follicular lymphosarcoma (generalized) *	1
(?) Giant follicular lymphosarcoma (localized)	2
Reticulum cell lymphosarcoma	7
Lymphosarcoma, unclassified	1
Hodgkin's disease	1
Lymphocytic cell lymphosarcoma or simple lymphoma of the iris	1
Total	21

* Leukemia developed in the course of generalized disease.

TABLE 7.—*Lymphomatous Tumors Reported by Reese*[20] *(1951)*

	No.
Lymphocytic cell	18
Reticulum cell	17
Lymphoma	14
Giant follicle	9
Hodgkin's disease	2
Unclassified	1
Total *	61

* Total includes the 20 cases reported in this paper.

TABLE 8.—*Sites of Lymphomatous Tumors of the Eye**

	No.
Lacrimal gland	7
Subconjunctival	5
Lids	5
Orbit	3
Total	20

* One patient with lymphoma in the iris alone, reported in 1942, was lost to follow-up after 14 years; her case is not included in these 20 cases.

TABLE 9.—*Survival Rates for Tumors Primary to Region of the Eye and for Tumors Generalized Before or at Same Time as Appearance of Eye Tumor*

	No.	No. Alive
Tumors primary in region of the eye	14	..
	No.	No. Alive
Tumor remained localized	7	4
Tumor later spread	7	1
Tumors generalized before or at same time as eye	6	..
Alive	..	0
Total	20	0

TABLE 10.—*Survival of Twenty Patients with Lymphomatous Tumors of Eye*

	1942	1954
Patients alive and without evidence of tumor	10	4
Patients alive with tumor	5	1
Patients dead	5	15
Total	20	20

Table 8 lists the sites of the lymphomatous tumors.

Table 9 presents data on the 14 tumors primary in the region of the eye. Seven of these remained localized, and seven spread later. Six of the patients had generalized tumors before or at the same time as appearance of the eye tumor; all of these six patients are dead.

Table 10 shows that in 1942 there were 10 patients alive and without evidence of tumor, whereas in 1954 only 4 were alive and without evidence of tumor. Five patients were dead in 1942; 15 are now dead.

TABLE 11.—*Data on Patients Still Alive*

	Patients	
	Still Alive	Percentage
Patients still alive in 1954	5 of 20	25
Patients with tumor primary in region of eye	5 of 14	28.5

If a patient with a single localized lymphoma around the eye survived more than 3.6 years, he survived an average of 16.0 years.

TABLE 12.—*Survival Rates Lymphomatous Eye Tumors According to Cell Type*

Cell Type	No. of Cases	Survival, Yr.
Lymphocytic cell	8	13.6
Giant follicle	3	13.0
Reticulum cell	8	7.2
Hodgkin's	1	4.0

TABLE 13.—*Average Survival Rates*

Rate for all 20 patients	10.25 yr.
Average age of patients at onset	55.5 yr.

	No.	Average Survival, Yr.
Tumors primary in eye region	14	13.0
Tumors remaining localized up to 1954 or to death from other cause	7	16.0
Tumors primary in eye region with later general spread	7	9.86
Disease becoming general after local eye tumor	7	3.6
Tumors generalized before or at same time as eye tumor	6	4.6

Table 11 shows that all the patients who are now alive had their tumors primary in the region of the eye. The survival rate of 25% is very high for a 15-year follow-up, but it must be remembered that in this small series a difference of one or two patients makes quite a percentage difference. As Stout [12] has pointed out, 2 to 3% of all patients have a long survival irrespective of the degree of involvement or of the treatment given. One of our patients illustrates this point very well. A man aged 55 had had bilateral subconjunctival tumor dating back to 1924. Biopsy in 1939 showed lymphocytic cell lymphosarcoma. The patient was treated with x-rays. He died in 1950 of coronary occlusion. I supposed that he had had complete regression of the subconjunctival tumors, but his son, who is a physician, recently told me that the tumors never entirely disappeared. I have, then, to state that the patient with the longest survival had multiple, that is, bilateral, subconjunctival tumors which were never completely eradicated. Another

patient, a dentist, who was treated by Dr. Arnold Knapp, by expression of the lymphoid tumors with forceps, has survived 15 years, without any x-ray therapy whatever.

The figures show that if a patient in this series with a localized lymphoma around the eye survived more than 3.6 years, he survived an average of 16 years.

Table 12 shows the survival rate according to cell type. There is no doubt about the difference between the survival rate for the lymphocytic cell and that for the reticulum cell type. The giant follicular type behaves like the generalized form, with a long course, and eventual death, after changing to another cell type. The single case of Hodgkin's disease adds nothing significant except that it is a rare occurrence in the region of the eye.

Table 13 shows the average survival rates. It is to be noted that a tumor primary in the region of the eye which remained localized had the best prognosis, and that all the tumors primary in the region of the eye also have a rather favorable outlook. The last two lines of Table 13 show that tumors which became generalized after local appearance in the eye and tumors which were generalized before, or became generalized at the same time as, the onset of the ocular tumor both had short intervals.

In 1942 I stated that the subconjunctival lymphomas presented an interesting group and had behaved in benign fashion, although histologic sections from these tumors could not be differentiated with any degree of accuracy from some sections from patients known to have generalized disease. I stated that extensions of the follow-up period to 10 years would help to clear up the status of these subconjunctival lymphomas. Three of the five patients are still alive, but one has required treatment as late as January, 1953. The fifth patient had what was probably a reticulum cell lymphosarcoma and died after 6 years, while the other four lived for 26, 15, 14, and 13 years, respectively. One of these died of coronary occlusion, after 26 years. None of these developed leukemia. All the reports in the literature show subconjunctival lymphomas to be the least malignant of ocular lymphomas. However, it should be noted that the clinical appearance was the same for those who died as for those who lived, and that the histologic appearance is also unsatisfactory for prognostic purposes.

SUMMARY AND CONCLUSIONS

Nothing new concerning the cause of lymphomas has been added, but there is a little more evidence that they are not all neoplastic from the onset. The figures regarding incidence and survival rates in the literature are extremely variable.

Classification of the lymphomas is as difficult as ever, but recognition of the various forms as interrelated, and often transitional from one type to another, makes one satisfied with less rigid, less formal classification. Much progress has been made with regard to numerous, variable, and interrelated potentialities of the reticuloendothelial system in the formation of tumors.

When lymphomas are generalized, tissue biopsies, complete blood counts, and bone marrow studies should be made at frequent intervals to serve as a guide treatment, to provide further information as to the transitions from one cell type to another, and to clarify our knowledge of the leukemias.

Lymphomatous tumors should be treated as though localized until proved otherwise. Combined surgical and x-ray therapy is recommended. Five eyes were removed, and cataract was known to be present in two other eyes. Keratitis sicca was severe in two cases. These complications of radiation therapy are now avoided.

Twenty patients reported in 1942 have been followed to 1954, making a total follow-up period of 16 years. Five of these are still alive; one of these required treatment in January, 1953. Five of the 20 patients died of conditions other than lymphosarcoma, after an average of 15.5 years.

These figures, although from a small series, indicate that the prognosis in lymphomatoid disease about the eye is not as poor as is generally believed.

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BETA RADIATION CATARACTS

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FOR ABOUT 14 years beta radiation from radium and radon has been used successfully in the treatment of certain external ocular conditions because of the relatively superficial effects and accurate localization of the radiation. Only recently, cataract has been reported [1] following the extensive use of beta radon in two eyes with severe vascularizing keratitis, and personal communications from other clinics have substantiated the possibility of this complication. In 1950, Friedell, Thomas, and Krohmer [2] reported the use of another source of beta radiation, Sr^{90}-Y^{90}. The depth dose of the beta particles of Y^{90} is comparable to that of radium and radon, and therefore it is not surprising that Wilson * and von Sallmann [3] independently reported that clinical and histologic changes in the lens could be produced in the rabbit eye by the Sr^{90} applicator. Because this applicator is commercially available to many physicians, it becomes more important to investigate the cataractogenic potentialities of beta radiation therapy.

It is the purpose of this paper (1) to determine the minimum cataractogenic dose of radon and Sr^{90} in rabbits; (2) to describe the type and progressiveness of the lens opacities produced; (3) to report the results of follow-up examinations of the lenses of those patients previously treated with beta rays, and (4) to reevaluate the clinical indications and dosages of beta radiation therapy.

BETA RADIATION CATARACTS IN RABBITS

Materials and Methods.—A total of 32 pigmented rabbits, weighing 4 to 5 lb. (1.8 to 2.3 kg.) and about 3 to 4 months of age, were anesthetized with pentobarbital (Nembutal) sodium intravenously, and their eyes were proptosed between the lids to obtain steady fixation. The kidney-shaped beta radon applicator previously described [1] was applied over the inferior limbus or the central cornea of the left eye, the maximally active surface of the glass radon needles in contact with the globe being about 5 by 7 mm. The right eyes were exposed similarly, using a Sr^{90} applicator † with an active surface 5 mm. in diameter and a surface output of 104 rep per second. The depth doses for this type of applicator are given by Tracerlab as follows: 1 mm. — 50%; 2 mm. — 25%; 3 mm. — 12%; 4 mm. — 6%; 5 mm. — 3%, and 6 mm. — 1.3%. Examinations for lens changes were made after maximal dilatation of the pupil to 8 to 10 mm. with 10% phenylephrine (Neo-Synephrine) hydrochloride and 3% atropine. The American Optical Company Giant-

From the Department of Ophthalmology, University of Illinois College of Medicine.
Read before the Section on Ophthalmology at the 103rd Annual Meeting of the American Medical Association, San Francisco, June 24, 1954.

* Wilson, F. M.: Beta Radiation Cataracts Reported in Rabbits Using the Sr^{90} Applicator, presented before the Chicago Ophthalmological Society, April, 1952.

† Tracerlab RA-1A strontium applicator, slightly modified to have a smaller active surface and higher output than the commercial model. Physical measurement of output was made by Tracerlab before and after the experiments.

scope and the Keeler ophthalmoscope with the +12 D. lens and varying of the distance of the observer from the eye were found to be the most effective means of detecting small lens opacities, especially at the equator, and no advantage was found in using the slit lamp, even for opacities posteriorly. A considerable amount of time, practice, and consultation among the three observers was necessary to detect some of the finest dust-like opacities. At suitable intervals, certain of these eyes were enucleated for histologic study by ordinary section, using the celloidin technique and hemotoxylin-eosin stain.

Results.—The ophthalmoscopic appearance and relationship of the vacuoles and opacities in the lens to the other structures of the rabbit eye are depicted in Figure 1.

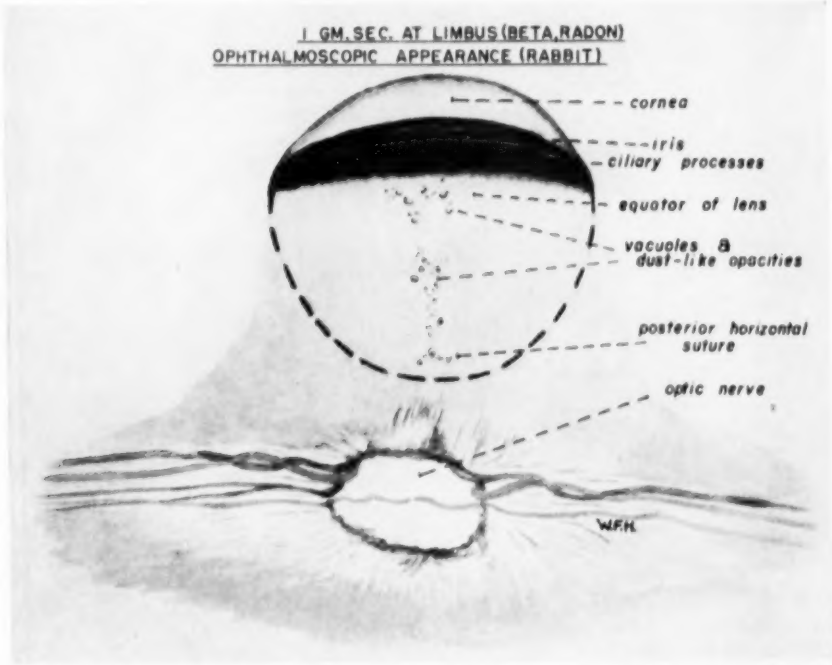

Fig. 1.—Panoramic view of the rabbit lens and fundus through a widely dilated pupil with an ophthalmoscope. By means of an extremely oblique view and with a +12 D. lens, the ciliary processes and equator of the lens are visible. The lens opacities followed exposure of the limbus to 1 gm.-sec. of radon six months previously. The dotted line encloses the area depicted in subsequent figures, showing the location of the posterior horizontal suture relative to the disc.

No qualitative differences could be detected between the eyes exposed to radon and those exposed to Sr^{90}. The latent period before the appearance of lens vacuoles and granules varied directly with the dose (Fig. 2)—as soon as two weeks after exposure of the limbus to 5 gm.-sec. of radon and one month after 5,000 rep of Sr^{90}. Threshold cataractogenic doses of 0.2 to 0.5 gm.-sec. and 500 to 1,000 rep did not produce granules until four to five months after exposure.

After exposure of the limbus, vacuoles and granular opacities developed directly under the area of treatment. A striking conformation of the area of the lens changes to the shape of the respective applicators was noted—a large, oval area for the kidney-shaped radon applicator (Fig. 3*A*) and a smaller, round area for the Sr^{90}

applicator (Fig. 4*A*). These opacities were seen in the far periphery, just posterior to the ciliary processes, apparently in the subcapsular region of the equator of the lens (Figs. 3*A* and 4*A*). In subsequent months, these opacities assumed a triangular shape, with the base at the periphery and the apex directed posteriorly (Figs. 3*B* and 4*B*). This apex then progressed as a band or thin line posteriorly, at which point the opacities and fine vacuoles seemed to fan out along the posterior horizontal suture (Figs. 1 and 4*C*). A few eyes, especially with the lower doses, did not develop equatorial vacuoles beneath the treated area; instead, the first opacities were first detected about four months later in the region of the posterior suture (Fig. 5). In a few eyes treated with larger doses, some vacuoles appeared beneath the treated area in the anterior subcapsular region (Fig. 6*C*), but these showed no tendency to migrate.

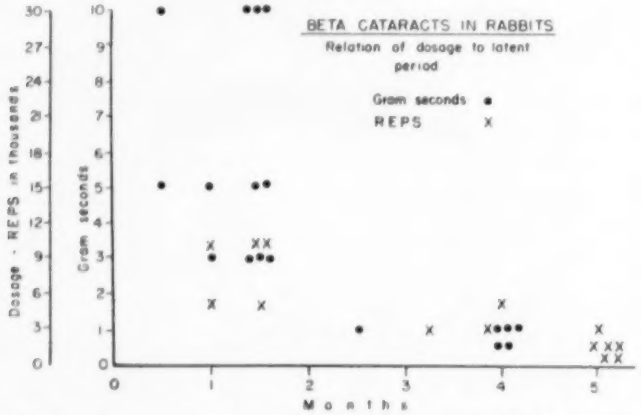

Fig. 2.—Relation of latent period to dose of beta radiation before the appearance of lens opacities.

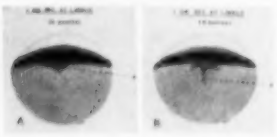

Fig. 3.—*A*, triangular area of lens vacuoles (*a*) at the equator, immediately beneath the area of limbus exposed to the kidney-shaped radon applicator three months previously. *B*, migration of lens opacities posteriorly (*a*).

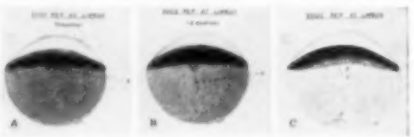

Fig. 4.—*A*, small round area of lens vacuoles at the equator (*a*), immediately beneath the area of limbus exposed to the 5 mm. round Sr^{90} applicator three months previously. *B*, migration of lens opacities posteriorly (*a*). *C*, further migration of lens opacities posteriorly, spreading out along the posterior horizontal suture line.

Those eyes which were irradiated over the center of the cornea presented a somewhat different picture. After a somewhat longer latent period, opacities appeared in the region of the posterior pole or off-center from it, with a subsequent migration of the opacities, so that they surrounded the posterior horizontal suture. The density of the opacities corresponded directly with the doses (Fig. 6*A* to *C*), and there was a greater tendency to the development of anterior subcapsular vacuoles (Fig. 6*C*). A nebular corneal opacity developed after exposures to 25,000 rep (Fig. 6*C*), the minimal doses being those producing any change in the cornea

clinically (M.I.D., or minimal inflammatory dose, as defined by Wilson). With doses of 30,000 rep, vacuoles appeared in the equatorial region, in addition to those at the posterior suture and the anterior subcapsular region (Fig. 7). The lowest dose of beta radon applied to the center of the cornea was 10 gm.-sec., which

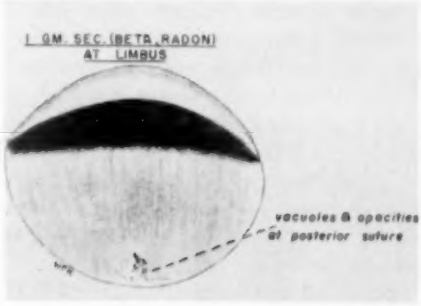

Fig. 5.—Lens opacities only at posterior horizontal suture, six months after exposure to 1 gm.-sec. of radon at limbus.

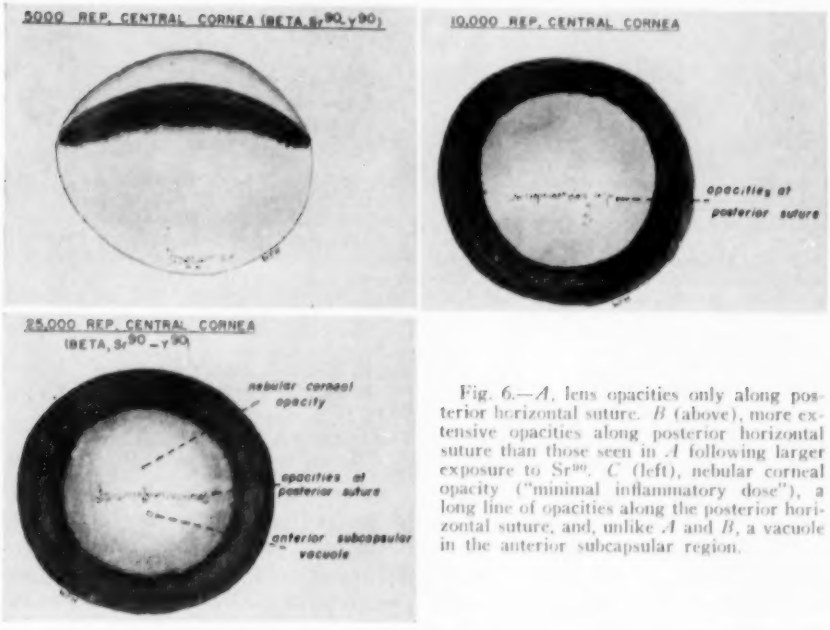

Fig. 6.—*A*, lens opacities only along posterior horizontal suture. *B* (above), more extensive opacities along posterior horizontal suture than those seen in *A* following larger exposure to Sr^{90}. *C* (left), nebular corneal opacity ("minimal inflammatory dose"), a long line of opacities along the posterior horizontal suture, and, unlike *A* and *B*, a vacuole in the anterior subcapsular region.

resulted in a corneal opacity with central ulceration, and rather dense accumulation of opacities along the posterior suture of the lens.

Eight months after irradiation, a crescent-shaped dark area was first noted in the irradiated area just peripheral to the opacities (Figs. 7 and 8). When the observer moved from an oblique position viewing the equator of the lens to a central anterior-posterior view, the shadow-like crescent moved centrally and the underlying lens opacities came to lie beneath (Fig. 8*A* and *B*). This indicated

that the crescent was located away from the equator and anteriorly. A clear halo was present peripheral to this, probably indicating new lens fibers. An interesting sequence of observations was made on one eye which was exposed to 5,000 rep at the limbus. The first detectable opacities after four months were granular in type and located at the posterior pole, and no equatorial changes were visible at this time. However, eight months after irradiation, the shadow-like crescent appeared peripherally and the posterior polar opacities were unchanged (Fig. 8*C*).

Histologic Findings.—The rabbit eyes were sectioned in an anterior-posterior direction, so that one side of the lens represented the exposed area beneath the irradiated limbus and the opposite side of the section served as an essentially non-irradiated control. In Figure 9*A* to *E* are depicted the changes six months after exposure of the limbus to 10,000 rep of Sr^{90}. The clinical appearance and progression of these opacities were similar to, although slightly severer than, that shown in Figure 4*A* to *C*. On the nonirradiated side of the lens, the equatorial cells of the germinal epithelium and the lens bow were normal (Fig. 9*A*). In the irradiated area (Fig. 9*B*), the nuclei of the lens bow were scattered in both anterior and posterior directions. Beneath the posterior capsule of the nonirradiated side, the normal acellular appearance and normal cortex were present (Fig. 9*C*). However, on the irradiated side, many nuclei of various sizes and shapes and disorganization of the adjacent cortex were present (Fig. 9*D* to *E*). In the other eye of this

Fig. 7.—*A*, appearance, following a relatively large exposure of the central portion of the cornea to Sr^{90}, of a crescent-shaped opacity or "shadow" near the equatorial region (*a*), in addition to opacities extending to the posterior pole and a vacuole in the anterior subcapsular region (*b*).

Fig. 8.—*A*, oblique view of lens, showing (*a*) crescent-shaped "shadow" opacity, peripherally, and (*b* and *c*) vacuoles, located posteriorly between the equator and the posterior horizontal suture. *B*, anteroposterior view through pupil, showing how (*b* and *c*) vacuoles depicted in *A* appear to have moved up under the crescentic "shadow" (*a*). Peripheral to the "shadow" is clear lens. *C*, granular opacities along posterior horizontal suture, which appeared first at four months (*b*), and later development of "shadow" opacity at eight months (*a*).

rabbit, comparable histologic changes were produced only on the irradiated side of the lens six months after exposure to 5 gm.-sec. of beta radon at the limbus. Sections of the eye exposed to 1 gm.-sec. at the limbus, whose clinical course is presented in Figure 4, showed nuclear changes and migration posteriorly similar to those which followed exposure to 5 gm.-sec., with perhaps less cortical change. Histologic study of the eye exposed to 3,000 rep at the limbus, and whose clinical course was shown in Figure 3, revealed very little scattering of the lens bow, but a few aberrant cells were found at the posterior pole, without much change in the surrounding cortex.

The histologic appearance of the crescent-shaped "shadow" opacity noted clinically after eight months is shown in Figure 10*A*. In addition to the scattering of nuclei at the lens bow and posteriorly, a crescent-shaped homogeneous zone of pink-staining material is located between the lens nucleus and normal peripheral cortex, and extends about equal distances anterior and posterior to the equator. On the edge adjacent to the nucleus are deposition of pigment granules (stain not

indicated) and cataractous changes in the cortex. These changes are not seen on the opposite, untreated side (Fig. 10*B*).

The only human cataract in our series available for histologic study was that in a 45-year-old man who, five and one-half years previously, had been treated for a severe vascularizing keratitis with 39 gm.-sec. of beta radon applied mainly at the limbus during a period of 34 weeks. Within a year prior to the beta radiation therapy, he had also received about 400 r with a radium plaque and 900 r of x-rays (130 kv.) at another institution. Five years after the last beta radiation

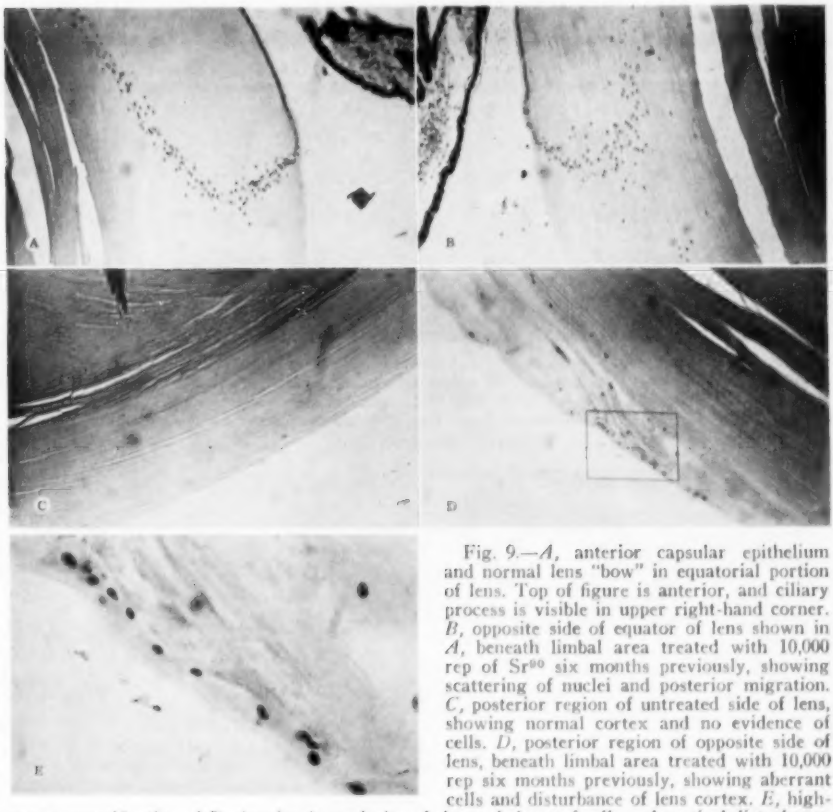

Fig. 9.—*A*, anterior capsular epithelium and normal lens "bow" in equatorial portion of lens. Top of figure is anterior, and ciliary process is visible in upper right-hand corner. *B*, opposite side of equator of lens shown in *A*, beneath limbal area treated with 10,000 rep of Sr^{90} six months previously, showing scattering of nuclei and posterior migration. *C*, posterior region of untreated side of lens, showing normal cortex and no evidence of cells. *D*, posterior region of opposite side of lens, beneath limbal area treated with 10,000 rep six months previously, showing aberrant cells and disturbance of lens cortex. *E*, high-power magnification of *D*, showing irregularity of size and shape of cells and cortical disturbance.

treatment, these developed a posterior subcapsular, granular, amber-colored opacity, without any detectable equatorial vacuoles when examined through a slightly hazy cornea. After an initial drop in vision from 20/25 to 20/80, further increase in the cataract was slow during the next six months. Intracapsular cataract extraction was performed uneventfully, and histologic section showed posterior subcapsular cells, some balloon cells, and extensive disorganization of the cortex (Fig. 11*A* and *B*), not unlike the findings in beta radiation cataracts of rabbits.

Minimum Cataractogenic Dose and Equilibration of Radon and Sr^{90} Dosages.—The term "minimum cataractogenic dose" is somewhat arbitrary, as pointed out by Cogan and associates.[4] First, the term "cataract" is usually used clinically to

denote an opacity sufficient to reduce vision, although relatively dense peripheral opacities or vacuoles may occur after irradiation over the limbus which do not obstruct a view of the central fundus. Accordingly, in this study, "cataract" is taken to denote any pathologic opacity in the lens. The second difficulty with determination of the "minimum cataractogenic dose" is that the difference in the physiologic presence of a few dust-like opacities scattered along the posterior horizontal suture line and the development of minimal pathologic opacities may be indistinguishable and dependent upon the method of examination and perseverance of the observer. Accordingly, in this study, only opacities which were not detected on early examinations, were seen on at least two occasions, and seemed more pronounced than normal variations were considered as "cataracts." Third, the "mini-

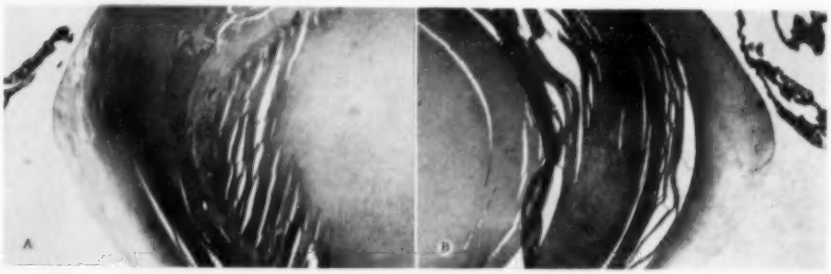

Fig. 10.—*A*, histologic appearance of crescentic "shadow" opacity, first appearing eight months after exposure to 3 gm.-sec. of radon at limbus, located between equator and nucleus anteriorly (*a*), probably representing liquefied cortex. The nuclear spots are artifacts. *B*, opposite, untreated side of lens shown in *A*. The lens bow and cortex are normal, the elliptical slits being artifacts.

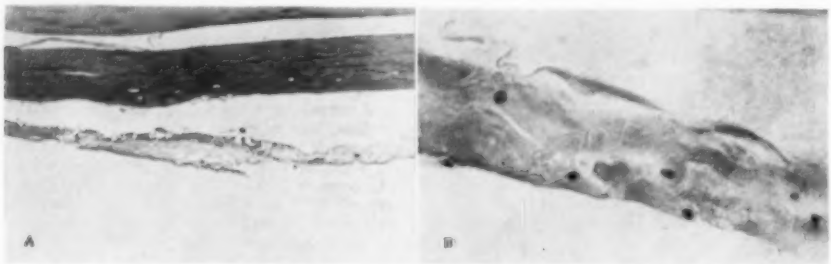

Fig. 11.—*A*, posterior subcapsular area of human lens, exposed six years previously to 400 r of radium plaque and 900 r of x-rays, and five years previously to 39 gm.-sec. of radon in divided doses over a period of 34 weeks, showing abnormal cells and cortical changes. *B*, high-power view of *A*.

mum" cataractogenic dose will vary indirectly with the age of the animal, and perhaps with other factors, such as individual and species differences.

With these qualifications in mind, the minimum cataractogenic doses in our rabbits exposed over the limbal region was about 500 rep, although other rabbits, exposed to 1,000 rep, did not show significantly more opacities (Table 1). Definite posterior sutural opacities were obtained in two eyes exposed to 0.5 gm.-sec. By relating gram-seconds to rep (see below) and, by extrapolation, considering the results from smaller doses of rep (Table 2), the minimum cataractogenic dose of radon applied over the limbus of the rabbit is found to be probably about 0.2 gm.-sec.

An attempt to equilibrate the rep output of the Sr^{90} applicator with the gram-seconds of the radon applicator biologically on the lens was done in three ways.

1. An estimation of the intensity of the opacities with various doses of each applicator indicated an approximate relation of 1 gm.-sec. to 3,000 rep (Table 1). 2. A comparison of the two applicators was made on the two eyes of the same animal to eliminate individual variability (Table 2). Considering the two animals in which the lesions were identical and the seven animals in which the radon produced only slightly more intense opacities, the ratio was found to vary from 500 to 5,000 rep per gram-second, with an average of 2,000 rep per gram-second. This range of variability between the two eyes of the same animal was especially large for the 1 gm.-sec. comparisons. 3. The relation of dosage to latent period (Fig. 2), excluding doses of over 5 gm.-sec., suggests that 2,000 rep per gram-second pro-

TABLE 1.—*Estimation of Intensity of Lens Opacities* vs. *Dosage of Beta Radiation at Limbus*

				Intensity of Opacities				
							Equatorial	
	Dosage	No. of Eyes	Average Grade	None 0	Posterior +1	Polar +2	+3	+4
Sr^{90}, rep./sec.	500	3	1.0	1	1	1	..	..
	1,000	4	1.0	1	2	1	..	..
	3,000	3	2.3	..	..	2	1	..
	5,000	3	2.7	..	..	1	2	..
	10,000	3	3.0	..	..	..	3	..
Radon, gm.-sec.	0.5	2	2.0	..	..	2	..	..
	1	4	2.2	..	..	3	1	..
	3	4	3.0	..	..	..	4	..
	5	4	3.3	..	..	..	3	1
	10	5	3.8	..	..	..	1	4

TABLE 2.—*Comparison of Cataractogenic Properties of Radon* vs. *Sr^{90} in Both Eyes of Same Rabbit*

Sr^{90} (R.E.)	Radon (L.E.), Gm.-Sec.			
Rep	0.5	1.0	3.0	5.0
500	+	+	+++	.....
1,000	0	±	++±	+++
3,000	..	+	++	++
5,000	..	0	+	.....
10,000	..	..	.....	+; + (2 rabbits)

0 means that R.E. and L.E. have lens changes of equal intensity.
+ means that radon-treated lenses have denser opacities than Sr^{90}-treated lenses.

duces similar latent periods at the higher doses and 3,000 rep per gram-second at the lower doses.

In summary, the cataractogenic relationship of our radon and Sr^{90} applicators would appear to range from 2,000 to 3,000 rep per gram-second. The ability to produce a nebular but persistent corneal opacity with these applicators was found to be 10 gm.-sec. and 25,000 rep, respectively, indicating a relationship of 2,500 rep per gram-second. In view of the similar depth doses of these two applicators, the similarity of the corneal and lenticular values is not surprising.

The question arises concerning the relative importance of the beta and gamma emanations from radon in the production of cataracts. A series of 20 additional rabbits were irradiated with the radon applicator, the beta particles being screened out by 1 mm. of silver. After five and a half months, thus far, only one cataract has been produced with doses as high as 64 gm.-sec. This was a posterior sutural cataract.

The eyes have not been followed sufficiently long to determine the degree of progressiveness or regression of the cataracts. However, two eyes exposed to 1,000 rep developed minimal opacities around the posterior suture at five months, and such opacities could no longer be seen at eight months. In general, the degree of opacification showed less change once the opacities had reached the posterior pole.

BETA RADIATION CATARACTS IN HUMANS

Seventy-three radon-treated eyes, in which the cornea was sufficiently clear to allow study of the lenses, were reexamined through a widely dilated pupil. Of these, 45 had definite radiation opacities and vacuoles; 13 had questionable opacities, and 15 had no radiation opacities. The changes were in every respect similar to those seen in the rabbit experiments, usually consisting of a wedge-shaped formation of granules and vacuoles beneath the treated area, with the base at the equator and the apex directed posteriorly. They were so characteristic that, in two

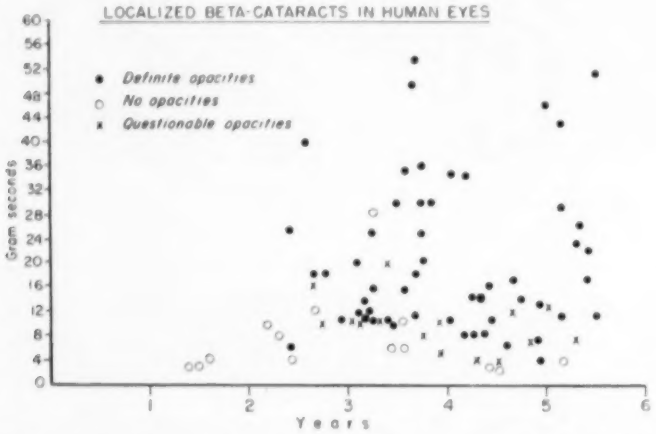

Fig. 12.—Time after treatment when lens opacities were detected following beta-radon therapy. This graph does not accurately represent the true latent period before the first appearance of the opacities.

patients, the shape of the opacity could not be explained by the treatment given in our clinic. Further investigation showed that these patients had been given beta radiation at another hospital in sufficient dose and in proper location to explain the shape of the opacities. In some patients with cortical opacities typical of senile cataract, the presence of typical beta radiation vacuoles could be distinguished. In two eyes previously reported,[1] the cataracts became mature and were extracted uneventfully except for a small persistent filtering bleb in each eye. The third cataract which required extraction (Fig. 11) remained moderately stationary for many months as a posterior subcapsular opacity, but it should be noted that this eye had previously received about 900 r of x-rays, which probably contributed to the development of the cataract. In three additional eyes, it was considered that the beta radiation opacities might have contributed to a reduction in vision. In these six eyes the total dose ranged from 43 to 53 gm.-sec. In the remaining 39 eyes the radiation opacities have not as yet contributed to any reduction of vision. It should be emphasized that many of these finer lesions after small doses could

be detected only by wide dilation of the pupil and examination of the peripheral lens with a brightly illuminated ophthalmoscope.

The relation of the latent period and the dosage cannot be determined accurately from our study, because these early radiational changes were not searched for at regular intervals after treatment. Figure 12 represents the time after treatment when careful reexaminations were made specifically for cataracts. Because of the localized nature of beta irradiation, widely separate areas of treatment on the same eye were recorded separately on the graph. The earliest opacities seen were after 29 months, and the smallest dose was 4 gm.-sec. No opacities resulting from the use of Sr^{90} have been detected as yet, but the maximum follow-up period is only 18 months. With radon and Sr^{90} depth doses comparable, and with the data on the relative cataractogenic doses using these two applicators in rabbits, it is anticipated that some of the early cases treated with Sr^{90} may develop lens vacuoles later.

TENTATIVE RELATIONS OF CATARACTOGENIC DOSES OF RADON AND SR^{90} IN RABBITS AND HUMANS

Although much of the mass of data is incomplete and will have to be revised after more accurate and absolute standardization of the applicators and the accumulation of additional biologic data, it is of some practical importance to estimate

TABLE 3.—*Tentative Relationships of Cataractogenic Doses of Beta Radiation*

Location of Radiation	Rabbit		Human	
	Sr^{90}, Rep	Radon, Gm.-Sec.	Sr^{90}, Rep	Radon, Gm.-Sec.
Limbus				
Minimal posterior sutural opacities.....	500-1,000	0.2-0.5	2,000-4,000 (?)	0.8-2.0 (?)
Vacuoles and opacities at equator.....	3,000-5,000	1-2	?12,000	4
Central Cornea				
Minimal posterior sutural opacities.....	5,000-10,000	(?2-4)	20,000-40,000 (?)	8-20 (?)
Vacuoles and opacities at equator.....	20,000	(?10)	?	40 (?)

even approximate relationships of cataractogenic doses of various forms of radiation (e. g., radon, Sr^{90}, and x-rays), in different locations (limbal *vs.* central cornea), and in different species (rabbit *vs.* human). An attempt to do this is represented in Table 3. In general, it appears that the rabbit lens is at least four times as sensitive as the human lens. The lens apparently tolerates about 10 times the beta dose when applied to the center of the cornea as when applied over the limbus. A "safe," or noncataractogenic, dose in humans might be considered no more than four times that which produces barely perceptible dusty opacities along the posterior horizontal suture in rabbits, viz., 2,000 rep over the limbus, or 20,000 rep over the central cornea; or with a radon applicator of our type, 1 gm.-sec. over the limbus or 10 gm.-sec. over the central cornea. Vacuoles at the equator are certainly a risk with doses of 12,000 rep or 4 gm.-sec. applied to the limbus. This applies to single doses. The recoverability of the lens from irradiation is unknown, but because the abnormal and dead cells cannot be sloughed off outside the capsule, cumulative effects of repeated doses may be high, especially if the single doses are sufficient to cause nuclear fragmentation and changes other than inhibition of mitosis.

COMMENT

Pathogenesis of Beta Radiation Cataracts.—In the light of previous work presented in an excellent review by Ham,[8] an attempt to integrate the information from our studies seems inviting. The lens opacities in rabbits and humans follow-

ing beta irradiation with both radon and Sr^{90} applicators were essentially comparable in our study, and agree with previous reports in the literature for x-rays, neutrons, and beta particles. The moderately sharp localization of radiation from the Sr^{90} applicator, as to both area (5 mm. on surface) and depth (only 1.3% of the radiation penetrating as far as 6 mm.), provides a means of observing the origin of and progression of changes not afforded by diffuse irradiation of the entire anterior ocular segment and lens. The rather sharp localization of the beta radiation opacities and vacuoles directly beneath the area of the applicator suggests that the clinical opacities are most likely caused by direct hits or absorption of the electrons on the germinative epithelial cells at the equator of the lens, rather than by changes in the ciliary processes or aqueous, which presumably would result in more diffuse opacities. The migration of vacuoles and opacities from the equatorial region and lens bow posteriorly to the horizontal suture can be followed clinically in rabbits who received above a minimum cataractogenic dose, and these aberrant and abnormal epithelial cells are found histologically beneath the capsule at the posterior pole of the lens.

With lower doses of either radon or Sr^{90} applied at the limbus, the initial opacities appear first along the posterior horizontal suture line. In spite of this, it is likely that, even with threshold doses, the initial subclinical changes are in the active epithelial cells at the equator, for the following reasons: 1. Larger doses of beta radiation produce visible changes at the equator first, without any evidence of posterior suture line opacities, an effect which would be unlikely if the posterior portion of the lens were more sensitive to low doses than the equator. 2. Posterior polar changes are seen later than equatorial vacuoles. 3. The depth dose at the posterior pole (7 mm. from the surface of the globe) is much less than 1%, indicating that less than 5 rep of the "minimal cataractogenic dose" reaches this area. 4. Aberrant cells can be found in the posterior sutural region histologically in lenses where no equatorial vacuoles had ever been seen. It is quite likely that the opacities which first appear at the posterior horizontal suture in the rabbit following exposure over the center of the cornea also represent the end-stages of damage to the equatorial cells because of inaccurate centering of the applicator or spreading and scattering of the radiation. Larger doses applied centrally produced visible vacuoles in the equatorial region. Therefore it seems reasonable that the vacuoles and opacities, which may partly represent fragmented nuclei, initially produced at the equator, are then pushed by new-growing lens fibers posteriorly, where they align themselves at the terminus of the lens fibers or the posterior suture line. Overlying cortical changes take place with larger doses, resulting in clinical cataract, which obstructs vision.

The actual quantity of radiation at the level of the lens necessary to produce these changes is being clarified for the rabbit. Von Sallmann and associates [5] first emphasized by their measurements on rabbit and human eyes, which can also be made on a scale drawing of known anatomical measurements of the eye, that the equator of the lens is about 3 mm. from the surface of the limbus both in rabbits and in humans, and that the anterior capsule of the lens is about 4 mm. posterior to the center of the cornea. The depth doses of various Sr^{90} applicators vary in published reports from 7% to 16% at 3 mm. and from 4% to 6% at 4 mm. Taking 12% of our minimal cataractogenic dose of 500 to 1,000 rep applied to the surface of the limbus, we find that 60 to 120 rep reaches the equatorial cells. This is in striking agreement with the values of 75 to 150 r of 1.2 mev x-rays which Cogan and associates [4] found produced minimal changes in the rabbit lens.

Latent Period.—If the latent period before the development of any opacities can be related directly with the life span of the animal, it is interesting to calculate from our rabbit data the latent period which might be expected in humans. The human life span is about 15 times that of the rabbit (75 *vs.* 5 years). Accordingly, we might expect minimal posterior sutural opacities in the human lens after 5 × 15, or 75, months, or equatorial vacuoles after 1 × 15, or 15, months. Our present human data are not in conflict with this.

Clinical Use of Beta Radiation in Ophthalmology.—The dosages and cataractogenic potentialities of beta radiation described above must be considered in the clinical use of beta radiation on the eye. Are there still any indications for beta radiation in view of these dangers? Because of the localization of beta therapy, its use in certain conditions of the lids, such as vernal catarrh, would not jeopardize the lens. The radium D applicator, with a depth dose of only 10% at 1 mm., would not endanger the lens, although other deficiencies make it less effective in the treatment of certain corneal conditions, such as deep vascularizing keratitis. It might well be the treatment of choice for recurrent pterygium,[6] where the use of radium, radon, or Sr^{90} would be contraindicated except in unusual forms of very "malignant" recurrences.

Much evidence has accumulated that radiational cataracts can progress for a while and then become stationary, or, with very small opacities, regress. We have seen some evidence of this in our studies. This factor, together with the visual unimportance of a few nonprogressive peripheral vacuoles or dust-like opacities in the lens, might still permit the use of beta radiation to the globe in carefully standardized doses at proper intervals between treatments without undue risk of reduction of vision because of radiational cataract. On the other hand, certain conditions may even warrant the risk of cataract because of the visual disability caused by the corneal disease, e. g., severe vascularizing keratitis, vascularization complicating keratoplasty, and epithelioma.

SUMMARY

Studies on rabbit and human eyes exposed to beta radiation from radon and Sr^{90}-Y^{90} have shown the localized cataractogenic effect of these emanations in sufficient dosage. The threshold is lower when such ratiation is applied over the limbus, resulting in equatorial opacities and vacuoles which migrate posteriorly. Tentative cataractogenic dosage schedules are presented. This complication should therefore be considered in the clinical use of beta radiation on the globe.

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BURDOCK BUR OPHTHALMIA

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and
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THE AMERICAN burdock (Arctium minus; cocklebur), during the late summer and fall months, can be found in all of the 48 states. This common weed, often growing to the height of a man's shoulder, bears a profusion of hooklet-covered burs (Fig. 1). Enclosed within each bur are literally hundreds of extremely fine, sharply pointed, barbed bracts, or phyllaries (Fig. 2). Although finer than the average adult human hair, these bracts are very rigid and firm, easily capable of penetrating the conjunctiva, and even the tarsal plate. The unidirectional orientation of the barbs forces the burdock bract, once embedded, to burrow even deeper into the ocular tissues.

This minute bract is a particularly painful ocular foreign body. Its presence is characterized by severe ocular discomfort, foreign body sensation, photophobia, marked conjunctival hyperemia, stringy mucoid, or even pseudomembranous, conjunctival exudation, lid edema, blepharospasm, and pathognomonic abrasions of the corneal epithelium. Small granulomatous nodules will form about the embedded bract, usually present in the upper tarsal conjunctiva, if the foreign body is undetected for as long as five to eight days. They may be found in any other portion of the tarsal or bulbar conjunctiva and are even capable of intraocular penetration.

The severe ocular reaction is the combined effect of two separate components, one mechanical and the other toxic. The mechanical effect is due to the direct abrasion of the cornea by the projecting needle-sharp bract tip during eyelid movement. These abrasions are vertically linear scratches and are readily demonstrable to biomicroscopy. After several days of repeated trauma the linear characteristic of the abrasion becomes lost, the development depending upon the number and location of the phyllaries. The late corneal picture displays a nearly uniform, grossly visible, dense, superficial punctate staining. A toxic explanation is necessitated to account for the very severe conjunctival and lid reaction observed.

Bruhn,[1] confirmed by Gredsted's earlier study,* has demonstrated the presence of a water-soluble glycoside irritant in the burdock plant. A rather severe conjunctival reaction is produced by the subconjunctival injection of such an aqueous extract, simulating in all respects the reaction observed around an embedded bract. A severe iridocyclitis ensues from the anterior chamber injection of the extract. Oil extracts of the burdock bur, injected into experimental animals, were nontoxic.

The diagnosis is frequently missed by the physician, who may be unfamiliar with the ocular behavior of this common noxious weed. A suggestive history is usually obtained from the patient, who may recall sudden onset of a foreign body sensation in his eye while he was walking through a weeded field or cutting brush in the fall. The ocular symptomatology is progressive in its severity. A severe conjunctival hyperemia and lid edema soon occur. The visual acuity decreases with the development of corneal edema and mechanical trauma.

The position of the bract is frequently indicated by the location of the vertically linear abrasions of the cornea (Fig. 3). Ever-

From the Department of Ophthalmology, University of Michigan Medical School.

* Gredsted.[2] This report refers to a case with intraocular penetration and lesion on the iris.

Fig. 1.—Arctium minus: leaf and bur.

Fig. 2.—Microphotograph of the fine bracts comprising the burs of Arctium minus.

sion of the upper lid in the suspected area will reveal an isolated pinpoint adherence of stringy mucus. Removal of the mucous secretion and careful slit-lamp observation will disclose a fine, reddish-brown, protruding spicule; a small granulomatous nodule will surround the bract if it has been embedded for several days.

TECHNIQUE OF EXTRACTION OF BURS

Removal with the finest of ocular forceps is surprisingly difficult even though one real-

Fig. 3.—Linear vertical abrasions of cornea.

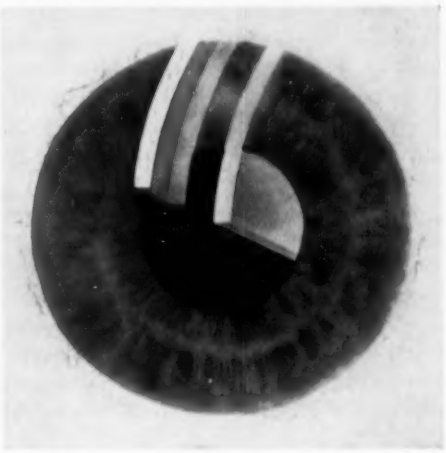
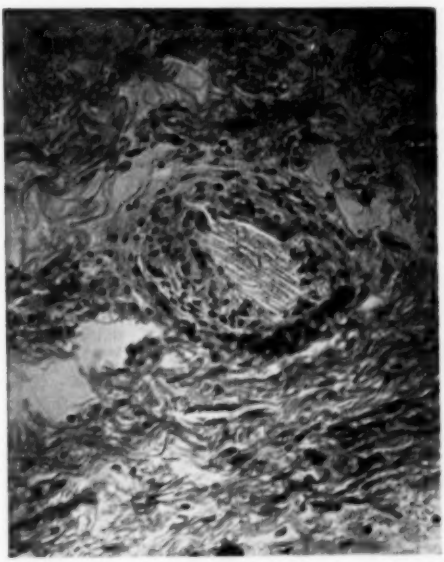


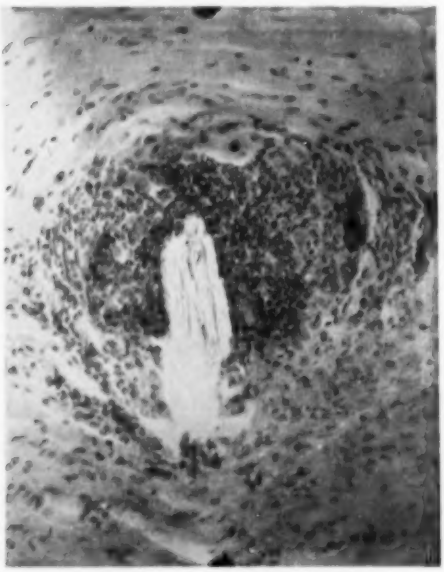
Fig. 4.—Photomicrograph of rabbit subconjunctival tissue presenting granulomatous reaction about foreign body 10 days after implantation of burdock bracts.



izes one is dealing with a bract of most minute size deeply "hooked" into the tarsoconjunctival tissue. This extraction has, in our hands, been greatly facilitated by the use of a watchmaker's mainspring forceps, an instrument which has extremely fine and accurately approximated tips. Topical administration of epinephrine 1:1,000 reduces the surrounding reaction and gives better forceps access to the exposed tip. Slit-lamp observation is indispensable during this extraction. Microscopic examination after extraction invariably shows the tough barbs to be intact. If the phyllary should break, or be too deeply embedded for forceps extraction, the small granulomatous nodule must be excised in its entirety.

In the average case the patient experiences immediate partial relief with extraction of the phyllary and requires only such prophylactic local antibiotic therapy as is customary in any corneal abrasion. The inflammatory reaction will disappear in three to four days, and healing may be hastened by topical cortisone. The presence of aqueous flare would indicate mydriatic therapy.

Fig. 5.—Photomicrograph of rabbit cornea showing reaction about burdock bract 20 days after implantation.



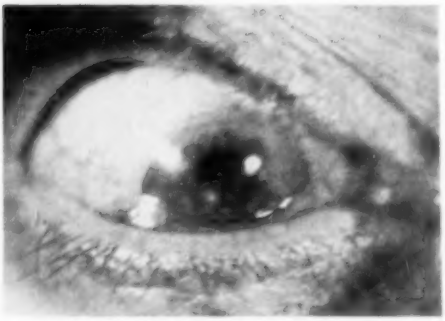


Fig. 6.—Appearance of human cornea three months after sustaining burdock injury with embedded bract.

EXPERIMENTAL PATHOLOGY

Subconjunctival implantation of burdock bracts in an albino adult rabbit eye resulted in a rather marked granulomatous reaction. The microscopic study of this granuloma revealed a lymphocytic infiltration, giant cell reaction, and pseudotubercle formation about the bracts.

Figure 4 is a photograph of the above-described tissue reaction, having developed in 10 days after subconjunctival implantation. Corneal stromal implantation in albino rabbits gave an identical type of foreign body tissue reaction, as illustrated in Figure 5.

REPORT OF A CASE

With one exception, the ocular burdock bracts we have seen have been embedded in the tarsal or bulbar conjunctiva. This patient, a 47-year-old white man, gave a history of trauma to the right eye by a "cocklebur" plant during a hunting expedition. During the subsequent three months he suffered from a chronic, sharply localized keratitis, which resisted all attempts at therapy.

Figure 6 shows the appearance of his eye when first seen by one of us (H. F. F.). The main lesion was a circular, grayish, elevated plaque with an umbilicated center, extending at least halfway into the stroma of the central cornea. The surrounding cornea was relatively clear. The conjunctiva and iris exhibited the usual inflammatory response expected in association with a corneal ulcer. Although it was not possible to detect a foreign body on initial slit-lamp examination, curettage of the lesion revea'ed a fine, tough bract embedded firmly in the umbilicated center of the scar. Within several days of this procedure the eye was stated to be more comfortable than at any time during the preceding three months.

SUMMARY

The common burdock plant is the source of very fine, barbed bracts, which produce marked symptoms as ocular foreign bodies. The ocular reaction is a combination of mechanical irritation from the sharp bract and chemical toxicity from a water-soluble glycoside. Effective therapy consists of slit-lamp recognition and manual removal of the bract.

Pathological reports are presented by courtesy of Prof. Carl Weller, Department of Pathology, University of Michigan Medical School.

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News and Comment

PERSONAL NEWS

Dr. Brittain Ford Payne Honored.—By unanimous vote, the members and officers of the Philippine Ophthalmological and Otolaryngological Society, during its annual business and scientific session, held in Manila, on Nov. 26, 1954, chose Dr. Brittain Ford Payne as an Honorary Fellow, in recognition of his invaluable help, friendship, and interest in the Society and its members.

GENERAL NEWS

American Association of Orthoptic Technicians.—The Association has received so many inquiries from ophthalmologists regarding the availability of orthoptic technicians that it has established a confidential placement service which will be of benefit to both ophthalmologists and technicians. Miss Laura B. Drye, Director, American Association of Orthoptic Technicians Confidential Placement Service, Eye and Ear Hospital, 230 Lothrop St., Pittsburgh 13, will be happy to assist any ophthalmologist to obtain a suitable orthoptic technician.

Treacher Collins Prize Essay.—Under this title, the Council of the Ophthalmological Society of the United Kingdom has instituted a prize of £100, awarded triennially, for the best essay submitted upon a subject selected by the Council.

The prize shall be open to qualified medical practitioners of any nationality.

The essay shall be written in the English language.

The subject for the next award of the prize is "Diseases of the Lacrimal Apparatus and Their Treatment."

The closing date for sending in essays for this award is Dec. 31, 1956. Essays should be submitted to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 45 Lincoln's Inn Fields, London, W.C.2, from whom also any further particulars can be obtained. No name should be on any essay, but a distinguishing pseudonym or quotation, which should be upon a sealed envelope containing the candidate's name and address, should accompany the essay.

Brooklyn Eye and Ear Hospital.—A Course on Glaucoma with particular emphasis on gonioscopy and study of the anterior angle will be given at the Brooklyn Eye and Ear Hospital on May 16, 17, and 18, 1955. Ample opportunity for practical instruction in the use of the gonioprism will be given, and material from the glaucoma clinic will be utilized.

The course will be given by Dr. Daniel Kravitz, assisted by Dr. Walter V. Moore, Dr. Mortimer A. Lasky, Dr. Harold F. Schilback, and Dr. Arthur Shainhouse.

Registration is limited to six ophthalmologists only.

Application and the fee of $40.00 may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

EFFECT OF PHENYLBUTAZONE (BUTAZOLIDIN) ON EXPERIMENTALLY INDUCED OCULAR INFLAMMATION

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PHENYLBUTAZONE is a synthetic drug recently introduced for the treatment of rheumatoid arthritis and allied disorders. It has therapeutic effects in some ways similar to cortisone and, like cortisone, induces sodium retention and edema. Since its administration is not accompanied by potassium diuresis, eosinopenia, or increase in ketosteroid excretion, it is considered unlikely that phenylbutazone acts directly or indirectly through the adrenal-pituitary axis.*

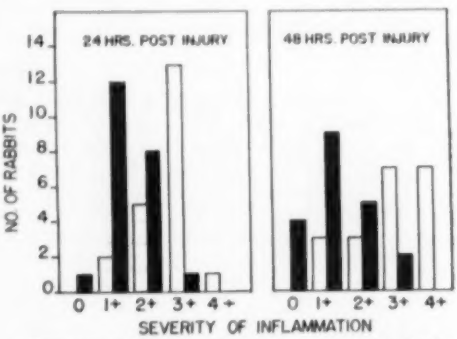
Woods † has reported that cortisone inhibits the ocular inflammation resulting from the injection of glycerin into the anterior chamber of the rabbit's eye. The study presented here was undertaken to determine whether phenylbutazone can also block this reaction.

METHOD

A transient chemical iritis was produced by the injection of 0.1 cc. of glycerin into the anterior chamber of the rabbit eye. The eye was first anesthetized with 1% tetracaine hydrochloride and the anterior chamber entered by a 26-gauge needle inserted at the limbus. One-tenth cubic centimeter of aqueous was withdrawn and replaced by glycerin.

The eyes were observed at 24-hour intervals and the degree of reaction recorded according to an arbitrary scale of 0 to 4+. A 1+ reaction was a minimal ciliary flush; a 2+ reaction was moderate ciliary reaction; the 3+ and 4+ reactions showed severe circumcorneal injection, but, in addition, the 4+ reaction showed varying degrees of conjunctival edema and hyperemia. In nearly all cases a transient corneal haze developed, which was due to endothelial damage and rendered slit-lamp observation unsatisfactory.

Fifty-eight rabbits with glycerin-induced iritis were used in these experiments. Twenty-two were given 100 mg. per kilogram of phenylbutazone by intramuscular injection every 8 hours, starting 4 or 5 hours before the glycerin injection and continuing for 48 hours thereafter. Eight were treated with 12.5 mg. of cortisone daily by intramuscular injection, starting three days before the eye injury, and 28 served as controls.



Severity of inflammatory reactions. Solid blocks show number of rabbits treated with phenylbutazone; open blocks show number of control rabbits.

In establishing the dose of phenylbutazone, it was necessary to take into account the fact that the drug is metabolized much more rapidly in the rabbit than in man, its biologic half-life being 3 hours in the rabbit and 70 hours in man.[6] When phenylbutazone was administered intramuscularly to the rabbit in a dose of 100 mg. per kilogram every eight hours, plasma levels ranged from 100 to 175 mg. per liter. These levels are comparable to those obtained in humans receiving a total daily dose of 800 mg. ‡

Phenylbutazone used in this study was supplied through the courtesy of Geigy Pharmaceuticals, New York.

This study was supported in part by the Public Health Research Institute of the City of New York and the Josiah Macy Jr. Foundation.

From the Research Service, Third (New York University) Medical Division, and the Department of Ophthalmology, Goldwater Memorial Hospital, Welfare Island, New York, and the National Heart Institute, National Institutes of Health, Bethesda, Md.

* References 1, 2 and 3.

† References 4 and 5.

‡ Estimations of plasma and aqueous levels of phenylbutazone were carried out by a spectrophotometric method previously described.[6]

RESULTS

In the controls an inflammation developed which usually reached a peak intensity (3+ or 4+) in 24 to 48 hours and then subsided over the next 3 days. By the 10th day all inflammation had disappeared.

A marked anti-inflammatory effect was observed in animals treated with phenylbutazone (Figure). Only 9% of the rabbits treated with phenylbutazone had severe reactions (Grade 3 to 4), as compared with 66% of the controls examined after 24 hours; after 48 hours, 22% of the treated rabbits showed severe reactions, as compared with 61% of the controls. The results were comparable to those obtained in rabbits given cortisone (Table).

Percentage of Eyes Showing Lesions of Grade 2 or Less Twenty-Four and Forty-Eight Hours After Injury

	Rabbits with Lesions of Grade 2 or Less		No. of Animals Used
	24 Hr. (%)	48 Hr. (%)	
Phenylbutazone-treated	91	78	22
Controls	33	29	21
Cortisone-treated	75	88	8
Controls	29	57	7

Analysis of the aqueous humor showed that phenylbutazone failed to penetrate into either normal or glycerin-injected eyes in spite of relatively high plasma levels (76 to 146 mg. per liter) and in the presence of a good therapeutic response.

To measure the effect of phenylbutazone applied locally, an ophthalmic ointment containing phenylbutazone (5% by weight) was applied to the irritated eye every three hours for three days, to three rabbits with glycerin-induced iritis. A control group of three rabbits was given the same ointment base not containing any phenylbutazone. An anti-inflammatory effect was not observed in the treated animals.

Two normal rabbits were given 0.1 cc. of 20% phenylbutazone subconjunctivally; this solution proved too irritating to be considered of further use.

COMMENT

The intramuscular administration of phenylbzutazone blocked almost completely the inflammation induced by the injection of glycerin into the anterior chamber of the rabbit eye. It is of interest that phenylbutazone exerts its effects in spite of its failure to penetrate into the aqueous humor in measurable amounts.

Demonstration of the anti-inflammatory effect of the drug required plasma levels comparable to those needed to obtain therapeutic results in patients with rheumatoid arthritis.[1]

To obtain effective levels of drug in a rabbit a daily dose of about 300 mg. per kilogram of body weight was needed. The dose is large as compared with the 10 mg. per kilogram which produces a satisfactory therapeutic response in subjects with rheumatoid arthritis. The large difference in dosage is necessary because the drug is metabolized about 20 times as fast in the rabbit as in man. Smaller doses of phenylbutazone than this gave neither a good blocking effect in the eye nor a satisfactory plasma level.

In view of the inhibiting action of phenylbutazone on glycerin-induced iritis in the rabbit, it would seem worth while to try this drug in man in certain inflammatory conditions of the eye. Some studies are available in the literature at the present time on the use of Irgapyrin (Geigy) a combination of phenylbutazone and aminopyrine. Bangerter, in Switzerland,[7] has reported good results with this combination in the treatment of acute and subacute iritis, keratitis, postoperative iridocyclitis, and traumatic cases. Von Hager,[8] similarly, reports good results in the treatment of 235 cases of iritis, iridocyclitis, dendritic and disciform keratitis, postoperative and traumatic reactions, scleritis, choroiditis, and optic neuritis. Kamal[9] reports on 11 cases; the drug was shown to be inef-

fective in two cases of advanced Behcet's syndrome, but good results were obtained in seven cases with postoperative iritis after extracapsular cataract extractions and in two cases of recurrent iritis of unknown etiology. Agarwal and Raizada report good results in 26 cases of iridocyclitis, scleritis, and keratitis.[10]

CONCLUSION

Phenylbutazone administered intramuscularly is capable of blocking the inflammatory effects produced by glycerin injected into the anterior chamber of the rabbit's eye, although it does not penetrate into the aqueous humor. The anti-inflammatory effect is comparable to that obtained with cortisone. It is ineffective used locally in an ointment.

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FURTHER DEVELOPMENT IN RETINAL PHOTOGRAPHY

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COLOR photography of the human and animal fundus is no new achievement. It was used by Wesley, Morax, and Reyburn in the 1930's [2] and has been used by many other workers since, both experimentally and clinically. But owing to the intensity of illumination required and the fact that the illumination must be concentrated to little more than a point, a carbon-arc source has been the illuminant usually chosen. This has always been notoriously unreliable for serial work, however.

For many years there have been feelings of concern among some ophthalmologists that harmful effects to the patient's eyes could result from the use of carbon-arc lamps, and, although this possibility has been strongly disputed by others, a constant search for an alternative light source has been conducted. None of those used, however, has provided every advantage sought for such an exacting piece of equipment.

Then the British Thompson Houston Company, of Rugby, England, produced a xenon-arc lamp (F. A. 5), with a spectral emission approximating daylight, which was successfully adapted to retinal photography in England.[1]

When the lamp was brought to Ohio State University for experimental use, however, it was discovered that the information gleaned with its purchase would need to be supplemented with exhaustive research to accommodate local electric currents, the equipment obtainable, and our requirements so far as reliability was concerned. Because of the need to use a retinal camera in an urgent research project on diabetic retinopathy, the Department of Electrical Engineering collaborated with the Department of Ophthalmology in building the necessary power unit for this project, and in four months this coordination produced the apparatus shown in Figures 1 and 2. The results obtained with the camera, a standard, but modified, Zeiss-Nordensen model, are shown in Figure 3.

The power unit designed to actuate the lamp and the camera shutter is in some respects essentially the same as that used by Hansell and Beeson, in England,[1] but with additional refinements to ensure that an operator will not expose a film too little or too much without being aware of it, or fail to get synchronization of the lamp flash and the shutter. Although this necessitated an increase in the bulk of equipment built into the unit, such a change seemed justifiable in the interests of heavy and prolonged clinical use over many years.

The exposure is revealed to the operator on a Beckman Decimal Counting Unit (Model 700), which registers up to 10 half-cycles, and if necessary repeats itself. A flash of 3 cycles' duration from a 60-cycle current gives, for instance, an exposure of 1/20 second, and the counter registers this. In the event of a wrong exposure, the counter shows it, and another exposure can be made immediately, instead of finding that this is necessary after the film has been processed. This eliminates the necessity of bringing patients back for further photography and also ensures that no transient retinal condition is lost by the delay required for color processing.

The xenon lamp is charged with 10,000 volts until the electrodes arc. The current is then reduced to 15 volts, 10 am. to keep the lamp arcing, and this illumination is used for

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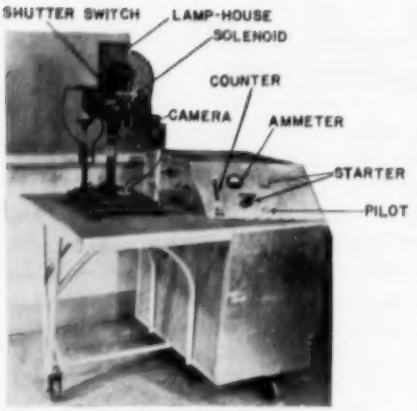

FIG. 1.

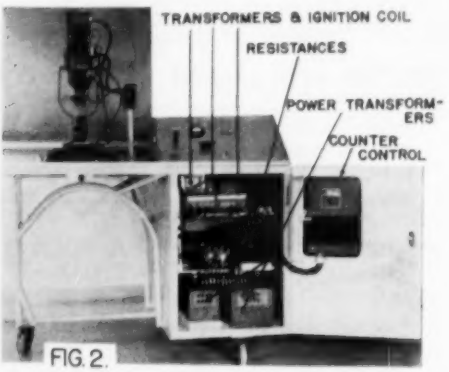

Fig. 1.—The Zeiss-Nordensen retinal camera modified and mounted on the power unit.
Fig. 2.—Door of the power unit opened to show the interior.

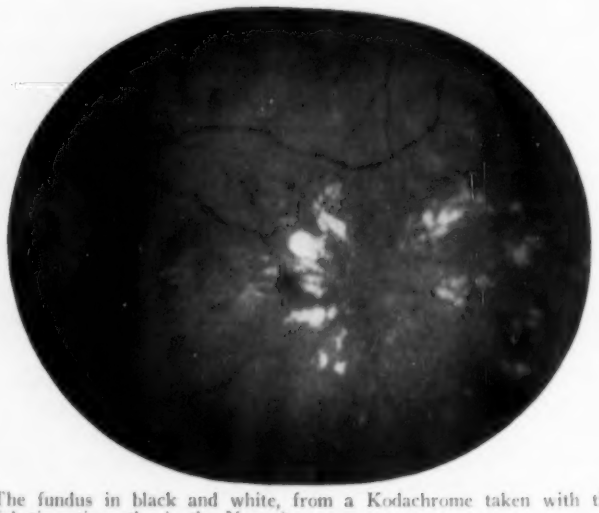

Fig. 3.—The fundus in black and white, from a Kodachrome taken with the equipment described (diabetic retinopathy in the Negro).

focusing the image of the retina on the camera screen. The light thus produced has been measured at 70,000 foot-lamberts at the eye position, considerably more than is required for focusing purposes; so a Polaroid filter in the shutter is used to reduce this to rather more than one-half.

When focusing is completed, a high current is fed to the lamp for 3 cycles, producing a flash of intense light for 1/20 second. The number of cycles can be varied to give a range of speeds of the order of 1/60, 1/30, 1/20, 1/15, and 1/12 second, while the camera shutter, set for 1/5 second, is open. Hansell and Beeson [1] used a shutter speed of 1/10 second and a flash of 1/25 second, but this was found a little unreliable when used with our synchronizing system; so the variable control, which when necessary would provide several different flash speeds, was incorporated into the unit. The longest exposure, 1/12 second, is of the order of the shortest exposure used in most retinal photography before the F. A. 5 lamp became available, but this slow speed is not normally used with the F. A. 5 lamp, only highly pigmented subjects demanding anything greater than 1/20 second.

The description of the operating details can be followed on the accompanying circuit diagram (Fig. 4). The xenon lamp (*P*) requires about 400 volts across its main electrodes, as well as a 10,000 volt tickler switch (*N*) in order to ignite. During starting, the switch (*M*) is held in the "start" position to provide the extra E. M. F. from the transformer (*B*). When the current begins to flow through the main electrode gap, the resistor (*D*) limits the warm-up current to about 12 am.

The circuit used by Hansell and Beeson included a high-capacity igniter coil, so that continuous current could flow through the tickler electrode for warm-up. This was tried

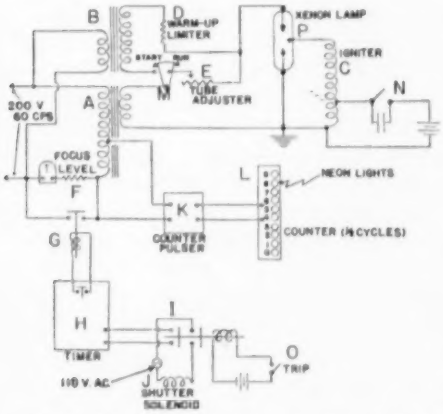

Fig. 4.—The principle of the circuit used in the power unit.

experimentally by us, but, the tickler electrode being so small, and the temperature of the electrode so high for this warm-up, a short lamp life, due merely to starting, seemed very certain.

After 20 or 30 seconds of warm-up, the spring-loaded switch (*M*) is released. This switch is so constructed that the upper electrode of the lamp cannot lose potential during the switching. If it did, for even a fraction of a second, the lamp would become extinguished. The temporary short circuit on the secondary of the transformer (*B*) is limited by the resistor (*D*).

During normal operation, the primary resistor (*F*) of the transformer (*A*) is adjusted so that the lamp current is just sufficient to be self-maintaining (about 5 to 6 am.). The voltage drop in the lamp is about 15 to 18 at this current level.

For pulsing the lamp at the high-energy level, resistor *F* is by-passed by the contactor (*G*), and the self-impedance of the transformer *A*, together with the lamp and the cast-iron grid resistor (*E*), is used to limit the lamp current to the desired level.

This high level is about 250 to 300 am., at which the lamp drop is about 25 volts. Currents greater than this tend to increase the size rather than the intensity of the arc, and, since the aperture of the optical system is a fixed size, arc sizes greater than those at the 300-am. level are useless. This was found by Hansell and Beeson also.

The timing circuit used is a standard General Electric semiautomatic weld timer, Nema type 1 – A, modified so that its maximum setting could not exceed 6 cycles in order to eliminate lamp abuse due to careless operating. This setting can be altered whenever desired. The trip relay (*I*) is double-poled, one pole being used to start the G. E. timer and the other being used to trip the Compur shutter on the camera. As already mentioned, the time constants are arranged so that the 3-cycle flash fits into a 10-cycle shutter opening. The shutter opens 3 cycles ahead of the flash, so that there is room for flash durations greater than 3 cycles whenever necessary.

In routine operation, the operator should always have some knowledge of the actual flash duration; so the counting unit, mentioned earlier, was chosen to provide a visual indication and record of this, and a full-wave thyratron circuit was used to develop the pulses needed to initiate the counter. The grids were negatively biased, and a signal voltage from the primary of transformer *A* was used to bring the grids back to firing potential.

During the focusing operation, the voltage across the half-primary of transformer *A* is only about 30 volts, but when the resistor *F* is by-passed, half *E* primary rises to about 100 volts. This means that the thyratron cir-

cuit is permitted to produce a counting pulse each half-cycle during flash conditions only.

It is possible to use a more accurate system, such as a synchronous weld timer with ignitrons for contactors, but the costs involved are rather prohibitive. Some of the equipment specifications are as follows:

A. G. E. Type M 3KVA wired 4:1 step-down

B. G. E. Type M 1KVA wired 1:2 step-up

C. Auto ignition coil

G. Aircraft 80A D. C. contactor

L. Beckman 700 – A, binary counter

The film used with this lamp is Kodachrome Daylight.

SUMMARY

A brief history is presented of the development of retinal color photography and of the adoption of the xenon-arc lamp for this purpose.

A method and circuit developed by us for this lamp, which at the same time provides safeguards against incorrect exposures, is described. Some of the equipment used is specified.

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Annual Reviews

CORNEA AND SCLERA

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ANATOMY AND PHYSIOLOGY

THE FINE structure of the rat cornea has been subjected to careful studies by Jakus [1] with the electron miscroscope, using very thin sections (100 A). Her attention has been directed especially to the interdigitating processes of the epithelial cells; the appearance, dimensions, and orientation of the collagen fibrils in the stroma; the filamentous component of the epithelial cells, and the structure of the corneal membranes. Descemet's membrane, even at this high degree of resolution, seemed to be structureless. The nature of the corneal canals has been studied by Friedman.[2] He made an attempt to verify the results of Magnus and Stubel by injecting hydrogen peroxide into the corneas of freshly enucleated steer eyes and concluded that the superficial and dry canals of Krassius, Magnus, and Stubel were artifacts. However, Friedman states that there is some evidence, especially if entoptic methods of investigation are used, that channels of some kind do exist. The question as to whether or not Bowman's membrane exists in rabbits has been the subject of considerable interest for many years. The general opinion has been that Bowman's membrane does not exist in rabbits; yet Yamamoto,[3] using phase microscopy and special techniques, has recognized a membrane similar to Bowman's, and in all probability there is a rudimentary form of this basement membrane even in rabbits.

The permeability of the cornea is reviewed most carefully and completely by Maurice [4] in an abridged edition of his thesis submitted to the University of London, 1951. The reader who is especially interested in this subject is urged to read this monograph in its entirety. Some of the author's conclusions which perhaps have a practical application follow: Under comparable conditions, the permeabilities of the limiting membranes to all ions of small molecular weight are similar, suggesting that ions pass across these membranes to the extracellular spaces. There is no unequivocal evidence of a directional or irreciprocal permeability of the cornea. It is not to be expected that this property exists to an extent that would make it readily detectable. The flow of aqueous humor through the limiting corneal layer is by theoretical expectation very low and has not been demonstrated by any satisfactory experimental techniques. There is perhaps a slight loss of water alone by evaporation from the corneal surface under normal conditions. In general the evidence suggests that the substances in solution in the corneal stroma exchange by passive diffusion with those in the plasma at the limbus and, within certain limitations, with those in the aqueous humor across the endothelium. It is probable that there is a small coexistent active transport of some substance out of the cornea which accounts for the maintenance of its normal thickness.

The most recent report of Potts, Goodman, and Johnson [5] is an extension of their previous experiments attempting to clarify the problem of corneal transparency. The authors give the results of their experiments on the transport of inorganic ions in the cornea. Potts previously demonstrated that the corneal endothelium is permeable to inorganic ions in both directions and suggests that secretion of inorganic ions into the aqueous might indicate the osmotic pump which maintains corneal dehydration and corneal trans-

parency. The authors summarize their work as follows:

1. After intracorneal injection of Na^{22} Cl, the sodium ion concentration of the cornea falls logarithmically and the concentration in the aqueous passes through a maximum. After 20 minutes, the concentration in the aqueous exceeds that in the cornea, but not that in corneal extracellular fluid.

2. Damage to the corneal endothelium, either mechanical or chemical, causes imbibition of water and clouding of the cornea, but no change in the behavior of radiosodium.

3. Damage to the corneal epithelium causes significant loss of sodium, but there is still more sodium entering the circulation via the aqueous.

4. In a dead animal there is still significant entry of Na^{24} from cornea to aqueous.

The authors offer the possible conclusion from these facts that sodium is actively secreted from the cornea into the aqueous, but that this movement has no direct connection with corneal dehydration.

Hydration and dehydration of the cornea and lens have received further study by Schwartz, Danes, and Leinfelder.[6] Through chemical and biochemical experimentation using bovine lenses and rabbit corneas, the authors attempted to affect the metabolism of the lens and the cornea and show that the weight gain, and thus the fluid uptake, is directly related to metabolic activity. Their conclusions were that the maintenance of a constant water content in these two structures is an energy-consuming process dependent upon the metabolic activity of the tissues. They conclude that energy is required to prevent hydration and dehydration of the tissue and that energy is also needed for the removal of water once it has entered as a result of defective metabolism. For detailed discussion of these significant papers, the reader is referred to the discussion by Potts, Kinsey, Leinfelder, Harris, and Smelser.

The corneal mucoid and its effect on corneal swelling and vascularization have been studied by François and Rabaey.[7] The mucoid of the cornea is basophilic and presents a metachromatic reaction with certain basic dyes. At the limbus this metachromasia disappears abruptly and almost completely, suggesting that the corneal mucoid is connected with corneal transparency. The authors produced corneal vascularization by intracorneal injections of turpentine and alloxan. As vascularization occurred, the total amount of mucoid was not decreased, but its concentration was reduced as the result of swelling of the corneal stroma. The authors conclude that a high concentration of corneal mucoid prevents penetration of vessels. When the concentration is reduced, as by swelling, penetration of the vessels is made possible.

The vitamin C content of cornea has been studied by Krwawicz, Seidler-Dymitrowska, and Vorbrodt.[8] Since vitamin C can be made visible by histochemical methods, its distribution can be studied. Normally the greatest concentration of vitamin C is in Bowman's membrane, under and in Descemet's membrane. In corneal degeneration intracellular vitamin C is decreased in the epithelium but is still present in the intercellular spaces. In phthisis bulbi the authors found no vitamin C to be present in the cornea. Kern[9] describes what appears to be an excellent apparatus for determining cations in small bits of corneal stroma. This apparatus has been used successfully in the Howe Laboratory.

Corneal sensitivity, with special reference to clinical methods of examination, is the subject of Boberg-ans' * doctor's thesis, submitted at the University of Copenhagen. He gives a complete summary of the previous work on corneal sensitivity, including 191 references. The article contains a review of the neuroanatomy of the orbit and the eye with reference to the sensory and vegetative innervation of the conjunctiva and cornea, and the microscopic appearance of the neurological elements in these structures. The different theories concerning the nutrition and the metabolism of the cornea are also reviewed. The author concludes that the

* Boberg-ans, J.: Corneal Sensitivity, with Special Reference to Clinical Methods of Examination, Thesis, University of Copenhagen, 1952.

method of von Frey is the most reliable clinical test of corneal sensitivity. He has substituted a nylon thread for a hair and uses a special holder permitting the length of the thread to be varied. All the theoretical considerations influencing these determinations are carefully discussed. The shortening of the nylon thread (by compression) should not exceed 5% of its length. The end of the thread (diameter of 0.11 mm.) will be able to cover 4 to 10 epithelial cells. To obtain maximum constancy of the stimulus, the speed of its application should be as low as possible. The author has also done considerable experimental work employing an air jet to examine the corneal sensitivity but does not find it superior to the use of von Frey hairs.

The neurotrophic changes in the cornea in cases of ophthalmic zoster and neuroparalytic keratitis were also studied. The findings are described in 27 patients who have had opticociliary resection. The author believes it is of great importance to the health of the cornea whether the localization of an interruption of the sensory nerves is retrobulbar, preganglionic, retroganglionic, or intramedullary. He further emphasizes that a lowered corneal sensitivity is often a most important symptom indicating serious disturbance in the nervous system.

Hart and Hinman [10] report on the treatment of corneal opacities by desiccation. When interstitial opacities in dogs were treated by a thorough desiccation of the cornea with dry air, the opacity often disappeared for a period of three to six weeks. The authors are hopeful that further investigation may demonstrate the value of this therapy.

CORNEAL HEALING AND CORNEAL REPAIR

Experimental Neuroparalytic Keratitis.—Sigelman and Friedenwald [11] report an excellent study of experimental neuroparalytic keratitis. They succeeded in producing sensory denervation of the adult rat cornea by an ingenious surgical approach through the roof of the mouth, whereby the ophthalmic branch of the trigeminal nerve could be severely injured without causing death of the animal. Their method consisted of pushing an especially built diathermy electrode through the roof of the mouth a distance of 4 mm. through the base of the skull. The operation could be performed in a matter of a few seconds, with the use of general anesthesia. The wink reflex was thereby completely destroyed, and its loss was used as the criterion of a successful operation. Pinprick wounds in the rat's corneal epithelium were then produced according to the method previously described by Friedenwald and Buschke. A fulminating and severe form of neuroparalytic keratitis resulted, which could be prevented by closure of the eyelids. Hence the keratitis is produced by exposure, but whether it is determined solely by absence of blinking or is aggravated by diminished lacrimal secretion was not determined. In the denervated cornea protected from exposure by lid closure, the mitotic rate was diminished approximately 20%, but the wound-healing activities of the corneal epithelium were normal. No histological abnormalities were noted in the corneal stroma, endothelium, or epithelium.

Smelser and Ozanics [12] have studied the effect of the Harderian and lacrimal glands upon regeneration of the corneal epithelium. Following the removal of the Harderian and lacrimal glands, they found a marked increase in the number of mitotic figures in the corneal epithelium. Removal of Harder's gland alone did not affect the number of mitoses, but extirpation of the lacrimal gland was followed by an increase in the number of mitotic figures. When the corneal epithelium of eyes lacking both tear glands was burned, the rate of epithelization increased greatly but the number of mitotic figures did not. Removal of the lacrimal gland alone did not affect the rate of epithelization; however, extirpation of Harder's gland alone shortened the time of healing of corneal burns. The effect of the latter operation was less than that obtained when both glands were removed. Topical application of homologous extracts of these glands did not affect the epithelization rate of regenerating corneal epithelium. Normal

luster of the cornea was lost after the removal of the lacrimal, but not the Harderian, gland.

An experimental study on the proliferation of limbal melanoblasts into the cornea following induced corneal lesion is reported by Michaelson.[13] The proliferation has certain features in common with vascular proliferation and occurs at the same time, perhaps as a result of the same stimulus. The melanoblasts which proliferate into the cornea tended to lose their pigment, especially under conditions of rapid proliferation. They quickly resume their capacity to form pigment under the influence of radiation.

Redslob and Brini [14] have studied the proliferation of the corneal endothelium and Descemet's membrane in pathological eyes. They point out that certain cases of glaucoma following perforating wounds with iridocyclitis may be due to obliteration of the angle by newly formed Descemet's membrane.

A histochemical study of the mode of wound healing in the cornea is reported by Ichikawa.[15] The author produces a sterile standard injury with a corneal trephine in the cornea of guinea pigs. After healing of the epithelium, granular cells from the subconjunctival limbus wander into the substantia propria of the cornea at the site of the wound. These granular cells seem to be mast cells, and enter the new-grown epithelium. The granules stain positively with the polysaccharide stain of Hotchkiss and show a metachromasia with the toluidine blue and thionine stain. The author also considers that the granules contain heparin and ribonucleic acid, but they do not contain glycerin.

Effect of Cortisone on Corneal Vascularization and Repair.—Ashton and Cook [16] devised transplantation experiments to investigate two questions of corneal vascularization, namely, vascularizing substances and alterations in tissue compactness. Their experiments failed to demonstrate any significant difference between normal and vascularized corneal extracts, or between normal and vascularized corneal grafts. A reduction in the compactness of the corneal tissue, whether produced mechanically or by the induction of corneal edema, may give rise to vascularization, provided the potential pathways resulting from the stromal separation communicate with the limbal vessels and are maintained sufficiently long. They found, furthermore, that destruction of the limbal vessels does not give rise to swelling or opacity in the cornea. They suspect suboxidation or anoxia of the corneal stroma as the direct stimulus to neovascularization.

The authors found that cortisone is able to restrain swelling of the cornea; they suspect that this action is a factor in the inhibition of corneal vascularization by cortisone. They also believe that cortisone is able to prevent an increase in capillary permeability, promoting vascular tone. This vasoconstrictive effect of cortisone on corneal vessels develops gradually and increases as cortisone administration continues.

Similarly, Langham [17] found that cortisone inhibits corneal vascularization, and he suspects that this effect may be due to the direct action of cortisone in restraining corneal swelling. He found no inhibitory action of cortisone on capillary endothelial proliferation. Langham [18] has used a neutralized solution of the organic compound alloxan to produce swelling of the cornea and subsequent vascularization. The substance was injected into the anterior chamber in varying concentrations, and a swelling up to three times the normal thickness of the cornea could be obtained. The swelling was reversible, and if the cornea was previously vascularized, the blood vessels seemed to become bloodless.

Similar experiments have been conducted by others. Ullerich and Durchschlag [19] produced standard lesions of the rabbit's cornea with the steam cautery of Wessely. They found that 1% cortisone, desoxycorticosterone, and 1% carbachol (Doryl) did not have an unfavorable influence on the epithelial regeneration. On the other hand, Wybar and Campbell [20] also produced standard heat injuries on the corneas of guinea pigs and rabbits and studied repair following injections of cortisone intraperitoneally. They are of the opinion that cortisone administered in

this manner causes a delay in the rate of epithelization and in stromal regeneration. Subconjunctival administration of cortisone in rabbits produced a marked diminution in new blood vessel formation within the cornea. The earliest local signs of cortisone intolerance are described by Martin and Dor,[21] who found a slight swelling and occasional desquamation of the epithelium in patients after the use of cortisone. These changes cleared immediately when the drug was discontinued.

Wound Healing and Repair.—The effect of various agents on the regeneration of corneal epithelium after experimental corneal wounds has received study by numerous authors. From the Wilmer Institute, Marr, Wood, and Grieves[22] report the results of their experiments. They use a technique devised by Buschke and Friedenwald in which the pH of the test solution is maintained at neutrality by Sorensen's phosphate buffer. It was found that polymyxin B sulfate, erythromycin, viomycin sulfate, carbomycin, and neomycin sulfate in the concentrations described did not delay healing of epithelial defect in the rat's cornea. Calsulfhydryl, in concentrations employed, showed no evidence of stimulating epithelial growth. Bruna[23] reports that estrone and progesterone, locally administered, accelerated the healing of sterile superficial and penetrating corneal wounds of the rabbit, while testosterone delayed the regeneration of connective tissue.

Ultrasonic Vibrations.—The effect of ultrasonic vibrations has received an increasing amount of interest in the ophthalmic literature. Haptén and Palm[24] studied the reaction of ultrasonic injury to the living corneas of 11 rabbits. The source was a standard Siemens Sonostat Jr. ultrasonic generator for 220 volts A. C., with an optimal output of 3 watts per square centimeter and a frequency of 800,000 per second. They found that a typical reaction developed, namely, that the visible vessels of the conjunctiva and iris dilated, while the pupil widened. With larger doses, a pronounced edema was observed in the cornea in the region of the application, and the conjunctiva became chemotic. The development of the vascular reaction was accompanied by an increase in the intraocular tension, which reached its maximum in 5 to 20 minutes after the end of the exposure and then decreased. Then the tension gradually fell to subnormal values, which persisted for several days. A flare developed in the anterior chamber, and trypan blue passed from the blood into the aqueous.

These changes correspond to the reaction of the eye to trauma previously described in the literature, particularly by Larsson (1930, 1932).

Schwab, Wyt, and Binder † have directed their investigations chiefly toward the effect of ultrasonics on corneal nerves of rabbits. One series of rabbits received 1 watt per square centimeter, an amount comparable to a therapeutic dose. Temporary granulation and fragmentation were observed, and sensitivity of the cornea was decreased for at least four hours. A second series of rabbits was treated with a high dose of 4 watts per square centimeter. There was immediate severe damage to all the corneal nerves exposed.

CORNEAL INJURIES

Lime Burns.—Lime burns continue to receive a good deal of notoriety, particularly as they are influenced by cortisone and allied substances. Rundles and Quinn[27] report four cases of severe corneal lime burns with recovery of full vision, which they attribute chiefly to the local application of cortisone. They also report considerable experimental work in which rabbits receiving their form of treatment are compared with controls, as well as animals treated with Hydrosulphosol or ammonium tartrate. In their opinion the use of cortisone locally appears to promote more rapid healing of all stromal infiltration and to decrease the inflammatory reaction to the alkali faster than either Hydrosulphosol or ammonium tartrate. There appeared to be no retardation of epithelial regeneration, and the authors feel that cortisone may even promote more rapid corneal epithelial regeneration. Their plan of treatment for this type

† References 25 and 26.

of injury includes the following: immediate thorough irrigation with water at the scene of the accident, sulfonamide or antibiotic preparations with local cortisone every two hours while the patient is awake, atropine and phenylephrine (Neo-Synephrine) if pupillary dilatation is poor, and monocular bandage with petrolatum (Vaseline) or a similar lubricant until all corneal staining has ceased. They also advocate moist heat three or four times daily until the eye is white. Attempts to neutralize the alkali with irrigations of weak acids have been found harmful, and they warn against the use of local anesthetic preparations.

The authors realize that their series of cases treated by this method is small and that the experimental data are limited. However, the method described seems reasonable and deserves a more extensive trial.

There does not appear to be complete unanimity of opinion regarding the effect of Hydrosulphosol on corneal and conjunctival lime burns, although most investigators are of the opinion that the treatment is ineffective. The rationale of Hydrosulphosol therapy is based on the presentation of an excess of the sulfhydryl group for local metabolism. Horwich and Turtz [28] investigated its effect on rabbit eyes which had been severely burned with sodium hydroxide. They found that the topical application of Hydrosulphosol produced no better results in a one-month period than might have been expected had no treatment been used. Similarly, Rocknem [29] believes that Hydrosulphosol is inferior in most instances to methylcellulose or castor oil in the treatment of controlled chemical burns of the cornea of laboratory animals. On the other hand, Alvaro [30] claims excellent results in the treatment of corneal burns, in ulcers and in the clearing of corneal opacities after topical application of Hydrosulphosol.

Other forms of treatment of ocular lime burns have been reported. Rinaldi [31] emphasizes that local spasms of vessels play a significant part in destruction due to burns. He uses a vasodilator, benzylamidazolin (Lambral), to prevent this angiospasm and cites favorable results in 62 cases. Early surgical treatment for severe chemical injuries is strongly advocated by Thies.[32] He recommends excision of necrotic conjunctiva, after which the denuded area can be closed directly or by a free graft from the opposite eye or from mucous membrane from other parts of the body. Damato [33] advises undermining of the conjunctiva, since a deposition of lime is usually retained beneath the conjunctiva in these cases. Its gradual absorption from this deposit gives rise to further severe injury. Corvasymton (oxyphenyl-methylaminoethanol tartrate) is an epinephrine-like substance applied in 10% solution. Its therapeutic value is ascribed to its vasoconstrictor action. By undermining the conjunctiva, this substance is allowed access to the lime deposit.

A unique case of an injury with beryllium from a broken fluorescent light bulb is reported by Flynn and Raiford.[34] In this patient several small foreign bodies were removed shortly after the injury. There was primary healing, but several episodes of recurring corneal erosion ensued. Healing was not complete for six months. There was a persistent haze of the corneal epithelium and considerable vascularization of the corneal stroma. Cortisone given topically had no effect on healing or on prevention of corneal erosion from recurring.

Karsch [35] reports 1,000 cases of keratoconjunctivitis due to hydrogen sulfide in a narrow valley in East Germany. There was severe irritation of the conjunctiva, with mild keratitis, but few significant after-effects.

Blodi [36] reports the fifth American case of delayed mustard gas keratopathy. The first symptoms occurred 21 years after the initial injury. The manifestations were not significantly different from the previous cases reported.

"Cat scratch keratitis" was observed nine times in 20 years by Sédan and Sédan-Bauby.[37] The seriousness of this condition is indicated by the fact that two eyes recovered completely, four recovered incompletely, and two required enucleation. The authors failed to demonstrate a bacterial cause for

these infections, but the use of oxytetracycline (Terramycin) and cortisone seems to have had a favorable influence in the cases recently seen.

The indiscriminate use of local anesthetics still seems to be a major source of serious corneal ulceration. Schmoger [38] reports five cases of severe corneal damage from the use of tetracaine (Pontocaine).

ULCERATIVE AND NONULCERATIVE KERATITIS

Pseudomonas Aeruginosa Ulceration.—Since P. aeruginosa is insensitive to the sulfonamides and antibiotics most commonly used, and since corneal infections caused by this organism tend to be extremely destructive, the subject of P. aeruginosa ulceration has received a more prominent place in the ophthalmic literature in recent years. Such a case was carefully studied and treated by Williams, Hench, and Guerry.[39] Full vision was regained after treatment with large doses of streptomycin subconjunctivally, intramuscularly, and topically. In addition, chlortetracycline (Aureomycin) was given orally. In vitro investigation of this organism showed it to be of a highly virulent strain. Polymyxin B was more effective in controlling its growth than polymyxin E or dihydrostreptomycin. These authors suggest that 50,000 units of polymyxin B be given daily by subconjunctival injections and polymyxin solution be instilled hourly. Ainslie [40] reports an excellent result in the treatment of P. aeruginosa infection of the cornea by subconjunctival injection of polymyxin E. He advises that the treatment be continued for several days after the initial clinical improvement.

Fraser [41] reports the cure of several hypopyon corneal ulcers by subconjunctival injection of polymyxin B.

Pirodda [42] reports the case of a 13-year-old boy who had a recurrent ulcer, apparently from P. aeruginosa, who recovered promptly with the use of oxytetracycline.

Lepri [43] describes three exogenous traumatic corneal infections, two with P. aeruginosa and one with Escherichia coli. Animal experiments indicated that different strains showed marked differences in their sensitivity to the same antibiotics, and the author makes a plea for early cultural determination of the responsible organism and rapid in vitro sensitivity tests.

Viral Keratoconjunctivitis.—Thygeson [44] summarizes the present status of our knowledge regarding viral keratoconjunctivitis and calls attention to two articles by Cockburn and co-workers. The United States Public Health Service has recently shown an increased interest in this subject, and ophthalmologists generally should welcome their aid and support in the study of these diseases.

Thygeson enumerates seven types of viral keratoconjunctivitis or conjunctivitis based on either clinical signs and symptoms or on laboratory findings. They are worthy of repetition:

1. Trachoma, because of its world-wide importance.

2. Inclusion conjunctivitis, which has shown a marked decrease in incidence, doubtless due to the action of sulfonamides and broad-spectrum antibiotics on the primary genitourinary disease.

3. Acute follicular conjunctivitis (Béal). This is occasionally seen in the United States but has only limited importance because of its short duration and the absence of corneal changes. It occurs predominantly in the summer, and in connection with swimming pools, and is one of three types of viral conjunctivitis known to be transmitted to swimmers.

4. Newcastle disease conjunctivitis, caused by a well-defined virus and transmitted from fowls to man. The disease, too, has minor significance because of its short duration and absence of corneal complications.

5. Epidemic keratoconjunctivitis, because of its widespread occurrence, and particularly because it is frequently transmitted through the ophthalmologist's office.

6. Herpes simplex cornea. This still remains the most frequent and the most serious

of this group of diseases. Thygeson again calls attention to the fact that the disease seems even commoner than formerly and the infection itself severer. This, in all probability, is allied to the general use of cortisone.

7. A relatively new type of keratoconjunctivitis, described by Cockburn and co-workers as the "Greeley type." This form has been reported in Missouri, Utah, and California, in addition to the original epidemic in Colorado. The infectious agent has not yet been isolated, but the occurrence of the disease in the late summer months, its predilection for children, the occasional neurologic features which accompany it, and, particularly, the similarity of the pharyngeal signs to herpangina, suggest to Thygeson that the disease may be due to one of the Coxsackie viruses.

Epidemic Keratoconjunctivitis.—A small epidemic of keratoconjunctivitis, involving nine patients, has been carefully studied by Cockburn, Nitowsky, Robinson, and Cheever.[45] These patients apparently were infected while attending a glaucoma clinic. The authors mention the occurrence of six small epidemics centered around other eye clinics in this country. In one small epidemic, the infection was maintained in patients with glaucoma for many weeks by transmission from patient to patient, probably by a tonometer. Serologic studies showed no relation between the diseases in two of the epidemics and the St. Louis encephalitis and the Sanders EK virus.

Wildi[46] reports unsatisfactory treatment of epidemic keratoconjunctivitis. Other authors report more favorable results. Sorsby, Ungar, and Crick[47] point out that chloramphenicol penetrates the eye readily when given subconjunctivally and advocate the injection of a 15% suspension. Such injections, combined with instillation of 1% ointment and 0.5% drops, have given good results in 26 cases of epidemic keratoconjunctivitis. Seventeen cases occurring in Japan are reported by Mori,[48] who believes that the incubation period is from 2 to 18 days. In infants the lesion appears as a membranous conjunctivitis associated with fever and severe stomach symptoms. In adults it originates as a follicular conjunctivitis, with preauricular adenopathy. Family transmission appears to be common in Japan, and punctate keratitis is seen in about 40% of cases. From West Germany, Thiel[49] reports that the antibiotic Tyrosolvin (a water-soluble preparation of tyrothricin and cetyl pyridinium chloride) instilled every two hours was of great value in the treatment of 80 patients.

Herpes Corneae.—Our lack of effective, specific therapy for dendritic keratitis is indicated by the many unrelated forms of treatment still advocated for this disease. Furthermore, the nonconformity of opinions regarding the type of chemical cauterization, and the extent to which it should be employed, indicates our general ignorance regarding the disease. Fink[50] and Orzalesi[51] point out that lysozyme is capable of inactivating the virus of herpes in vitro and that there is a clear relation between the lysozyme content of the blood, tears, and cornea and immunity to herpetic infection. These authors believe that the adverse effect of cortisone on herpetic infection is due to the fact that cortisone actually reduces the lysozyme activity in the blood and secretions. He treated 15 human cases of dendritic keratitis with drops of 2% lysozyme every four to six hours, but, in addition, he used light scraping of the base and margin of the ulcers and the instillation of penicillin drops. In 14 cases the eyes recovered in five to eight days, while in one other case the eye appeared to get worse. In still another case conjunctivitis appeared after eight days, which he interpreted as being an allergy to lysozyme.

Fazakas[52] recommends thiamine (vitamin B_1) and an antibiotic for the treatment of herpes corneae.

Reynon[53] reports favorable results in cases following the use of a subconjunctival placental implant. He claims good results especially when the implantation is made in the early stages of the keratitis.

The effect of antihistamines and cortisone was studied experimentally by Boles-Carenini and Cima.[84] These authors treated 28 rabbits with experimental herpes corneae by topical application of diphenhydramine (Benadryl) and antazoline (Antistin). The drugs were applied hourly for three days, and later every three hours. Cortisone ointment, 0.5%, was instilled in the same way. The authors noted no beneficial effect following the use of diphenhydramine and antazoline. Cortisone ointment had no curative effect, and they noted that in some instances it caused a spread of the infection to the corneal nervous system.

The most significant experimental work in herpes simplex which has come to my attention for several years is that reported by Hall, MacKneson, Ormsby, and Ormsby.[85] In order to determine the degree of humoral immunity resulting from a primary herpetic keratitis, they bled 14 rabbits before inoculation and at monthly intervals thereafter. The serum antibodies in the rabbits had reached a high level one month after primary inoculation, and reinoculation did not increase it. The antibody level was maintained for at least two months after the second inoculation. In order to study the effect of immunity resulting from primary herpetic keratitis in rabbits upon reinoculation of the same cornea, they reinoculated 66 previously infected eyes at intervals of from 3 to 24 weeks. It was possible to reinfect 42% of the eyes with the virus. The majority of these reinfections were manifested by mild keratitis, in marked contrast to the severe primary keratitis previously observed. In order to determine the effect of humoral antibody on a normal cornea in the immune animal, they inoculated the left eyes of 22 rabbits which had recovered from primary keratitis in the right eye after intervals of 4, 8, and 22 weeks. A typical primary type of keratitis developed in almost all the eyes despite the high level of humoral antibody. The residual corneal scarring in these eyes, however, was much less than that resulting from primary herpetic keratitis. In order to determine the effect of tissue immunity in the absence of humoral antibodies, they took full-thickness corneal grafts from 20 eyes which had recovered from primary herpetic keratitis and transplanted them into the corneas of nonimmune rabbits. Eight such grafts were reinoculated four weeks after transplantation. These grafted corneas failed to show any significant difference in the degree of keratitis between the graft and the host cornea. Seven of the eight eyes developed keratitis. The effect of combined humoral and adjacent tissue immunity on transplanted rabbit corneas was studied by taking 20 full-thickness grafts from nonimmune eyes and transplanting them into healed corneas which had recovered from the primary herpetic keratitis. Four weeks after transplantation, 10 grafts were inoculated with herpes simplex virus. The inflammatory reaction was minimal in both the graft and the host cornea, a result which was similar to that previously observed of reinoculation in healed eyes.

The authors conclude that circulating antibody in the rabbit plays a small, but important part in reducing the severity of herpetic keratitis. This is demonstrated by the reduction in residual scarring which occurs when the second eye of a rabbit is inoculated with virus after the first eye has recovered from a primary herpetic keratitis. The authors believe that local defense mechanisms play a major role in reducing the severity of herpetic keratitis. The failure of an immune cornea to retain its immunity when transplanted into a nonimmune host and the ability of a nonimmune cornea to acquire immunity when it is transplanted into an immune eye are of practical importance in keratoplasty. The authors offer as a possible explanation the replacement of the cells of the donor cornea by those of the host.

Interstitial Keratitis.—During the past year the general interest in interstitial keratitis has continued, doubtless owing to the controversy over the effect of cortisone on the disease. Klauder and Meyer[86] have a significant article based on work done at the

Wills Eye Hospital, in Philadelphia. They report the results of the treatment of 36 patients with acute syphilitic interstitial keratitis who received one or a combination of the following drugs: corticotropin, cortisone, thyroid extract, and testosterone. All other treatment except mydriatics was withheld in order to evaluate the effect of this treatment, but in some cases, out of consideration for the welfare of the patient, artificial fever and antisyphilitic treatment were used. The severity of the disease in their patients was classified as severe, moderate, and mild. Their results were compared with those of a previous report made by the same authors on 59 patients with acute interstitial keratitis treated with penicillin alone or with penicillin plus artificial fever.

Cortisone was used either by subconjunctival injection or by local instillation. Of 13 patients, 9 had recurrences; 1 of the remaining 4 was lost to observation, and 3 had no recurrence after observation for as long as one year. In mild and moderate cases there was a dramatic clearing of the cornea and subsidence of inflammation in as brief a period as 7 to 12 days, but because of recurrences this dramatic effect was not maintained. The authors are in accord with Woods that such a striking effect does not occur in severe cases of the diseases. In their cortisone-treated patients recurrences were not prevented by systemic treatment, regardless of whether it was given at the beginning of therapy or only after local use of cortisone was stopped. The authors believe that this observation suggests that the mechanism that brings interstitial keratitis to an end is consummated in the cornea and that cortisone does not assist this mechanism, but retards it. The authors seem to agree with many ophthalmologists, who have long maintained that interstitial keratitis is a self-limited disease and is but little, or not at all, influenced by antisyphilitic treatment. The authors regard cortisone of doubtful value in relieving the severer forms of interstitial keratitis, and since they feel that cortisone prevents the development of local immunity, they have discontinued its use in severe cases.

The authors uniformly find evidence of thyroid deficiency in patients with interstitial keratitis, and during the acute stage of the disease they give 2 or 3 grains (0.12 or 0.20 gm.) of desiccated thyroid daily, together with fever therapy. They have found that Pyrifer (a B. coli vaccine) is the most satisfactory fever-producing agent.

In spite of the fact that the authors regard antisyphilitic treatment of acute interstitial keratitis of little benefit to the cornea, they believe that the underlying syphilitic infection requires antisyphilitic therapy and employ it routinely. Penicillin combined with fever therapy has not given results superior to those achieved with metal chemotherapy and fever. They advocate alternating courses of oxophenarsine and a bismuth compound during the acute phases of the disease. After the keratitis becomes quiescent, a short period of antisyphilitic treatment with penicillin is used.

The authors have been interested also in the endocrine imbalance in interstitial keratitis and have used testosterone in the treatment of three females with the disease. They have not obtained any striking improvement from the use of testosterone, but they believe that further observation is required.

Cook and Langham [57] believe that in all cases of interstitial keratitis the thickness of the cornea is directly related to the virulence of the disease and that corneal vascularization is always preceded by corneal edema. Administration of cortisone subconjunctivally was followed by marked decrease in corneal thickness. They believe that corneal vascularization probably cannot occur without prior edema of the corneal tissue.

Mycotic Infections.—Fazakas [58] gives the result of his mycologic studies of disease of the anterior segment of the eye. Cultures for fungi gave a positive result in 253 (25.5%) of 992 subjects with normal eyes and in 820 (36.4%) of 2,210 patients with diseased eyes. In only 35 cases was the ocular disease entirely attributable to the mycotic infection. These were cases of mycotic keratitis, mei-

bomianitis, canaliculitis, blepharitis, and conjunctivitis. In another group, fungi played the part of secondary invaders and apparently may influence the course of a disease favorably or unfavorably.

Reiter's Syndrome.—Theodore [59] gives an excellent discussion of Reiter's disease. His studies support the recent experiences of others that cortisone and corticotropin are of value. It is claimed that the excellent response to these agents, coupled with the ineffectiveness of the antibiotics and sulfonamides, is evidence against a viral or bacterial etiology, and it suggests an allergic basis for the syndrome.

CORNEAL DISTURBANCES ASSOCIATED WITH METABOLIC OR SYSTEMIC DISEASES

Phlyctenular Keratoconjunctivitis.—Thygeson [60] states that it is generally recognized that phlyctenular keratoconjunctivitis is an allergic reaction to bacterial proteins, particularly to the proteins of the tubercle bacillus. In this connection, a clear analogy exists between phlyctenules of the conjunctiva and bacterids of the skin. He states that although the tuberculid is the commonest bacterid, dermatologists are all familiar with such other types as the moniliid and the trichophytid, which are due to sensitization to proteins from organisms other than the tubercle bacillus.

During a four-year period, Thygeson found 37 cases of phlyctenulosis in his private and clinic practice, 9 of which showed no evidence whatever of tuberculosis by direct or indirect testing. In a careful study of these cases, five were presumed to be due to pathogenic staphylococci. Two patients were coccidioidin-positive and tuberculin-negative. These two persons had lived all their lives in the San Joaquin Valley, where coccidioidomycosis is endemic. In one case the phlyctenulosis was believed to be due to hypersensitivity to Candida infection. Thygeson believes that these cases of phlyctenulosis represent a manifestation of bacterial allergy and that the phlyctenulosis is not produced by the allergens responsible for ordinary allergic conjunctivitis. Phlyctenules are rarely seen in hay fever conjunctivitis, or vernal catarrh; neither are they seen in other allergies, such as atopic dermatitis or drug idiosyncracies and, strangely enough, not in the allergies caused by the use of antibiotics. Thygeson concludes that, although allergy to tuberculosis is considered the most important cause of phlyctenular keratoconjunctivitis, rare cases appear to be due to allergies to other bacterial, viral, or fungal proteins.

Lemoine [61] is likewise of the opinion that phlyctenular keratitis is an allergic reaction of the cornea and is most commonly due to an allergy to tuberculoprotein. He further states that in 10% of the cases the disease is due to an allergy to bacterial toxins or to a hypersensitivity to food. He also includes interstitial keratitis as an allergic reaction to the toxins of the Treponema pallidum and attributes the good results obtained with fever therapy to the stimulating effect of the fever on glands of internal secretion, especially the pituitary and adrenal glands. He also mentions that patients with interstitial keratitis frequently have a deficient thyroid function.

Ocular Rosacea and Marginal Keratitis.—Borrie [62] has studied 133 patients with cutaneous rosacea and 99 patients with combined ocular and cutaneous rosacea. He believes that the disease does not spread from the eye to the face or vice versa. He has also found that the ocular lesions respond to x-ray therapy, while those of the skin do not. Another study of a similar corneal disease, namely, marginal keratitis, is made by Corkey,[63] who presents 22 cases. A striking number of his patients gave a history of arthritis. Corkey believes that riboflavin plays a special part in the metabolism of the avascular cornea and that when it is lacking, local asphyxia occurs, with necrosis due to toxic substances in the cornea. Goldsmith [64] believes that rosacea keratitis progresses independently of rosacea of the skin. He states that the commonest manifestation of ocular rosacea is a severe nodular keratitis and conjunctivitis which develops in the exposed interpalpebral region. The disease is commonest during the spring

and early summer, indicating that external allergens may precipitate an attack in an already sensitized eye.

Xerophthalmia.—Vaughan [65] reports three cases of xerophthalmia in infants occurring in California, the disease in one case being due to congenital bile duct atresia, and in the other two, to antiallergenic diets without proper vitamin A supplementation. Three additional cases of prexerosis in adults are described, two of them in association with chronic alcoholism, and the third, that of an adolescent boy, in association with general malnutrition. The author gives an excellent review of the subject, including the history of xerosis and its clinical characteristics, pathology, and treatment. Even though the disease is obviously rare in the United States at the present time, his report suggests that a number of cases may be overlooked, owing to lack of familiarity with the early ocular signs on the part of ophthalmologists and pediatricians. Vaughan urges that ophthalmologists be on the alert for evidence of avitaminosis A in infants with special feeding problems, in children and adults on reducing or antiallergenic diets, and in chronic alcoholics and patients with gastrointestinal and liver disease.

Parenchymatous Xerosis. — Twenty-five patients with this degenerative disease are reported by Agarwal.[66] The author advocates subconjunctival implantations of placenta and claims unusually good results, with numerous complete cures.

Keratoconjunctivitis Sicca. — During the past year Sjögren and his associate ‡ contributed two reports on the disease which bears his name. He describes a congenital deficiency in lacrimation and divides his cases into three groups: those due to a central disturbance, those due to a lack of innervation, and those with congenital aplasia of the lacrimal gland. He has tried corticotropin in the treatment of four cases of keratoconjunctivitis sicca, without any appreciable change in the clinical picture. A similar experience in the treatment of seven patients with a typical Sjögren syndrome is reported by Lepri.[69] After an immediate beneficial subjective effect, the symptoms recurred when treatment was stopped.

Band Keratopathy in Vitamin D Intoxication.—Gifford and Maguire [70] report an interesting case of band keratopathy in a 61-year-old white man, who during the treatment of rheumatoid arthritis was given 150,000 U. S. P. units of vitamin D daily for two years. This represented a total consumption of 109,500,000 U. S. P. units of vitamin D. The blood calcium was found to be 14.6 mg. per 100 cc. The authors conclude that the calcium deposits were a direct result of the hypercalcemia and warn that early corneal changes should serve as a warning of renal damage, which might prove fatal.

Ocular Pemphigus.—A brief, but excellent, review of our present knowledge of pemphigus is given by Back,[71] who compares the ocular disease with the skin disease. Some of the important points the author makes are the following: The occurrence of conjunctival vesicles is rare; the pathology is mainly subconjunctival, while in pemphigus of the skin the lesions are confined to the epithelium and do not necessarily form scars; ocular pemphigus is rarely associated with pemphigus of the skin, while it coexists commonly with lesions of the mucous membranes; corticotropin and cortisone have a morbidistatic effect on pemphigus of the skin, while they have no effect on pemphigus of the eye. Beasley and Shields,[72] likewise, describe this well-known clinical entity and believe that corticotropin and cortisone are of value only in the incipient stages of the disease.

Corneal Changes in a Case of Hepatitis.—Cristiansson [73] reports a case of epidemic hepatitis leading to chronic injury of the liver cells and persisting jaundice. Corneal dystrophy and decreased lacrimation developed. The author discusses its similarity and dissimilarity to keratoconjunctivitis sicca. His case differed from the usual keratitis sicca in that the precorneal film was of normal

‡ References 67 and 68.

thickness. There was also pigmentation of the limbus, unlike any seen in keratoconjunctivitis sicca.

Crystals in the Anterior Segment of the Eye.—Goar and De La Motte [74] carefully describe two cases of cystinosis in children with intractable rickets. The diagnosis was made by slit-lamp examination, which revealed innumerable iridescent crystals embedded in the superficial layers of the cornea. In one case the crystals were found in a stained specimen of excised conjunctiva. The importance of examining all infants who have severe rickets with the slit lamp is urged by these authors.

Doggart [75] points out that calcium phosphate crystals are occasionally evident in the cornea following lime burns, as well as occasionally in arcus senilis and arcus juvenilis. Cysteine crystals have been found in all layers of the corneal parenchyma in cases of juvenile renal rickets. Cholesterol crystals have been detected in primary lipid dystrophy, trachomatous keratomalacia, or keratomalacia from malnutrition, and in cases of marginal degeneration of the cornea. Crystals are frequently found in patients past 60, and tyrosine has been identified in many senile cataracts. They are a prominent feature of cataracts occurring in mongolism, myotonia atrophica, tetany, and thyroid deficiency. Crystals have also been identified in the anterior chamber, especially following hyphema or hypopyon, and secondary glaucoma has been precipitated by crystals in the anterior chamber.

CORNEAL DISEASES NOT ASSOCIATED WITH METABOLIC OR SYSTEMIC DISEASES

Hereditary Corneal Dystrophies.—Franceschetti [76] points out that if one wishes to classify the hereditary degenerations of the cornea, one must take into account the fact that the responsible mutation of genes not only can produce numerous intermediary forms but can create new types. Therefore, a proper classification must be one which can absorb such new types without changing the way in which it is set up. Franceschetti has an excellent classification, which bears reprinting in this review.

Classification of the Heredofamilial Degenerations of the Cornea *

I. Parenchymatous degenerations
  A. Classical forms (noncongenital, progressive)
    1. Dominant forms
      (*a*) Granular degeneration
      (*b*) Lattice-like degeneration
    2. Recessive form
      Macular degeneration
  B. Congenital forms (more or less stationary)
    1. Recessive form
    2. Dominant form
  C. Diverse forms
    1. Crystalline degeneration
    2. Primary fatty degeneration
    3. Primary calcareous degeneration (?)
    4. Cornea farinata
    5. Dystrophia filiformis profunda

II. Degenerations of the limiting membranes
  A. Anterior limiting membrane
    1. Recurrent hereditary erosions
    2. Juvenile epithelial degeneration (Meesmann's type)
    3. Juvenile degeneration of Bowman's membrane with epithelial changes
    4. Whorl-like corneal opacities (cornea verticillata)
    5. Mosaic-like ("crocodile-shagreen") degeneration
    6. Band-shaped degeneration
    7. Marginal degeneration
  B. Posterior limiting membrane
    1. Cornea guttata
    2. Polymorphous posterior degeneration

III. Combined forms (parenchyma and limiting membranes)
  A. Diverse combined forms
  B. Edematous dystrophies of the cornea
    1. Primary or essential edema of the cornea
    2. "Epithelial" degeneration of Fuchs

IV. Corneal degenerations in general affections
  A. Disturbances of lipid metabolism
    1. Lipochondro-osteodystrophy of Hurler
    2. Hand-Schüller-Christian disease
    3. Diverse affections
  B. Disturbances of intermediary protein metabolism
    1. Cystine diathesis
    2. Diverse affections
  C. Cutaneous affections
  D. Diverse affections

* Table by Franceschetti and Forni, (slightly modified).

He does not share the pessimism concerning keratoplasty in cases of corneal dystrophy. In the granular form of corneal dystrophy, a lamellar graft often gives favorable results. He calls attention to Paufique, who obtains good results with deep lamellar grafting. For the macular and congenital form, perforating

keratoplasty is indispensable for a good visual result. In the various forms of degeneration of Bowman's membrane, lamellar keratoplasty is the operation of choice. In the primary, fatty degeneration of the cornea, Franceschetti believes that keratoplasty in general is not very satisfactory. For Fuchs's epithelial dystrophy, he advocates the mushroom graft, although the results are often disappointing even with this method. Still, he has obtained useful vision in a number of cases.

Lorente [77] gives a detailed report on the pathological examination of a corneal section obtained in the course of keratoplasty from a patient with Groenouw's hereditary dystrophy. He found profound degenerative changes in the nerve fibers of the corneal parenchyma, which he believes support the neurogenic theory of origin of this disease.

Hereditary Polymorphous Deep Degeneration of the Cornea.—McGee and Falls [78] have studied two families certain members of which show a rare form of endothelial dystrophy of the cornea. A careful survey of the families showed that the condition is hereditary, and most likely congenital. It is to be differentiated from ordinary endothelial dystrophy of the cornea—cornea guttata. Koeppe (1915) first described this form of endothelial dystrophy and presented six cases. He thought that the concavities seen were congenital pits on the inner corneal surface. In 1920 he reported 18 similar cases and concluded that the lesions were of congenital origin and due to defective development of the endothelial surface. Theodore was the first to report cases of endothelial dystrophy in the American literature. He believes the disease to be congenital and suggests that endothelial dystrophy be considered to have two forms: one congenital and the other senile (cornea guttata). Berliner, in his discussion of Theodore's case, stated that the lesions on the posterior cornea were nodules or thickened depressions, rather than vacuoles.

According to McGee and Falls, polymorphous degeneration of the posterior limiting membrane is gene-determined and is apparently transmitted as a dominant trait with fairly good penetrance. It is the authors' belief that the disease is congenital and is nonprogressive or of very slow progression. They refer to Cuntz-Schüssler's observation on three successive generations as lending credence to this hypothesis. In their own cases a father and son had the disease, but the evidence is insufficient basis on which dogmatically to suggest dominant inheritance. The authors conclude that the condition is a specific entity and is to be differentiated from cornea guttata.

Primary Oleoguttate Central Superficial Degeneration of the Cornea.—This is a term proposed by Alajmo [79] for a bilateral lesion which he describes in a 39-year-old man. The slit-lamp picture was that of a degeneration with oily spheres, like that described by Lugli, but it differs in that the lesions were central and there were no other degenerative changes. The spots throughout the lesion were yellow and situated beneath the epithelium.

Hereditary Crystalline Degeneration of the Cornea.—This condition has been studied by Malbran, Paunessa, and Vidal.[80] The pathological material studied was removed by lamellar keratoplasty from a patient with such a degeneration.

Epithelial Corneal Dystrophy with Bullous Keratitis.—Barnshaw [81] described a case of Fuchs's epithelial dystrophy before the College of Physicians of Philadelphia. It concerned a 45-year-old man with this disease. Cowan's § discussion of this case is of some interest. He differentiates between Fuchs's epithelial dystrophy and endothelial dystrophy, noting that the former is rare and the latter common. Cowan has had under his observation many cases of endothelial dystrophy which have progressed to disintegration of the entire endothelium without the slightest indication of involvement of the anterior layers of the cornea. He does not believe that the endothelium acts as a barrier

§ Cowan, A., in discussion of Barnshaw.[81]

to prevent aqueous from entering the cornea, with subsequent edema. For many years he has seen eyes with total absence of endothelium which presented no surface edema whatsoever.

NEW AND UNCOMMON DISEASES OF THE CORNEA AND SCLERA

Nutritional Dystrophy of the Corneal Epithelium.—Nañagas [82] reports a series of 24 patients seen by him in the Philippines between September, 1950, and August, 1952, with what he calls "nutritional dystrophy of the corneal epithelium." The disease has its highest incidence in the age group of 21 to 40 years. It is associated especially with pregnancy and breast feeding, accounting, he believes, for its higher incidence in women. The dystrophy is characterized by grayish, superficial punctate opacities, giving a stippled effect to the surface of the cornea. The individual lesions vary in size from being barely perceptible to confluent pinhead-sized lesions. They have a predilection for the pupillary area and the lower half of the cornea. The early lesions are confined to the corneal epithelium, appearing as highly refractile nodules, slightly elevated from the surface. In advanced cases with permanent changes there is a sheet-like thickening of the epithelium, absence of Bowman's membrane, and thinning of the substantia propria. The lesions occur with signs and symptoms indicative of deficiency in vitamin B complex, namely, angular stromatitis and peripheral polyneuritis.

Bowen's Disease.—Four new cases of intraepithelial epitheliomas of the cornea are reported in the last year's literature. Willard [83] cites the case of a 60-year-old woman with such a tumor, confirmed by biopsy, which was treated by x-rays because of its large size. The author is of the opinion that irradiation is not satisfactory because of the relative insensitivity of the tumor to x-rays. In his opinion the preferred treatment is complete surgical excision. Gonzales Vanrell [84] reports three cases apparently well treated by excision, followed by wide cauterization of the base.

Ocular Ochronosis with Alkaptonuria and Osteoarthritis.—Cambiaso [85] reports the eighth case of this disease occurring in Argentina. He describes the typical triad, namely, pigmentation of the cornea and sclera, alkaptonuria, and osteoarthritis deformans.

Buphthalmos.—Laborne [86] reports the unusual occurrence of buphthalmos in four brothers, children of parents who are first cousins. He analyzes the problem of heredity and consanguinity, as well as the statistics from some of the great ophthalmological clinics. He concludes that buphthalmos is a rare disease occurring in 1.010% to 0.079% of all eye patients. He believes that consanguinity plays a more important role in buphthalmos than is generally recognized.

Chronic Glaucoma Occurring with Keratoconus.—D'Ermo [87] reports two patients, aged 64 and 70, respectively, with both chronic glaucoma and keratoconus. Both conditions were treated successfully in these patients.

Ophthalmia Nodosa.—Five new cases of ophthalmia nodosa due to caterpillar hairs are reported by Teulières [88] and Dreyer.[89] Teulières reports four cases due to caterpillars of pine trees, Thaumatopea pytiocampa, which are common in the region of Landes and Gironde during the months of February and March. The author suspects that these caterpillars have venom glands on their dorsal areas, and he believes that hairs contaminated with venom or that the venom alone may produce ocular injury. One of his four patients required enucleation of the eye. Dreyer's single patient had an initial stage of severe burning and photophobia immediately after the injury, which was followed by a nodular stage, characterized by alternating exacerbations and remissions of the inflammation. Dreyer's case is of interest in that a few months after the injury caterpillar hairs had migrated through the cornea and on to the iris, causing nodular iritis.

Scleritis.—Givner [90] describes four cases of scleritis, and he divides the disease into an anterior and a posterior type. The deeper

type of anterior scleritis is rarer than the superficial type but is much more serious.

Orbán [91] reports a rare form which he calls "scleritis progressive posterior." It occurred in two middle-aged men with chronic rheumatic disease and chronic unilateral uveitis, going on to blindness. Pathological examination showed the posterior sclera to be covered by granulation tissue. A chronic infiltrative posterior uveitis had spread into the sclera, causing it to become four to five times its normal thickness.

TREATMENT OF CORNEAL DISEASE

Medical Therapy

Irradiation.—Hughes [92] gives an excellent review of the indications and contraindications of beta irradiation, including his own experiences with the modern type of applicators. For details, this article should be read in its entirety.

Michaelson, Gluecker, and Stieglitz [93] produced standard thermal lesions in both corneas of 45 rabbits and gave low-voltage x-radiation on the resulting vascularization. The opposite eye of the same animal was used as a control. The authors found that 75% of the expected vascularization was inhibited. In their experiments with cortisone they found that the hormone was effective in inhibiting new-vessel growth to the extent of 65% of the expected vascularization. They conclude that radiation and cortisone in the doses usually used clinically are almost equally effective in inhibiting new-vessel growth into the cornea.

Three cases of carcinoma of the corneal limbus treated successfully with the Sr^{90} applicator are reported by Kaae.[94] In two the condition was diagnosed microscopically as parakeratotic carcinoma, while one exhibited epithelial hyperplasia with pronounced nuclear abnormalities, but definitely invasive growth. The author believes that the radiosensitivity of carcinoma of the limbus appears to be the same as that of skin carcinoma. Seale [95] reports a large experience with the treatment of carcinoma of the limbus by irradiation. He used beta radiation in 3 patients and gamma radiation in 16 others. The beta rays caused a rather intense postoperative reaction, and lens damage was noted in six patients. All his patients had incipient cataract before therapy, however. The author feels that lenses containing incipient cataract are more susceptible to radiation than normal ones.

Protection of the cornea against beta radiation with cysteine is reported by McDonald.[96] He elaborates on the work of Patt and associates (1949), who showed that cysteine hydrochloride given intravenously to rats was highly protective against 800 r of x-rays administered subsequently. McDonald also refers to the work of von Sallmann on the protective effect of cysteine on ocular lesions subsequently exposed to x-rays, so the author concludes that in rabbit eyes the subconjunctival injection of a total of 1 cc. of 8% cysteine (free base) in two areas protects the epithelium, stroma, and endothelium of the cornea against the application of 40,000 rep of beta radiation one hour later, the Sr^{90} ophthalmic applicator being used.

Cortisone, Hydrocortisone, and Corticotropin.—Woods [97] has thoroughly reviewed the use of corticotropin and cortisone in ophthalmology through 1952. His opinion regarding the use of these hormones may be summarized in the following statements: The inflammatory and exudative phases of disease are usually dramatically controlled by the parenteral administration of corticotropin or by the topical administration of cortisone. In degenerative disease these agents are totally without effect. Both agents give spectacular results in nongranulomatous uveitis due to allergy, toxins, or physical trauma. Their use is contraindicated in tuberculous uveitis.

The effect of both agents in experimental ocular disease is to inhibit the inflammatory response of the eye. There is a marked inhibition of cellular exudation and fibrosis, as well as impaired endothelial regeneration and neovascularization.

Yasuna, Ojers, Frayer, and Scheie [98] give an excellent report on their experimental study of the effect of cortisone on the eye and arrive at the following significant conclusions.

1. Cortisone instilled locally into the conjunctival cul-de-sac appears to be innocuous in doses up to 25 mg. per cubic centimeter.

2. When cortisone is injected subconjunctivally in a dose of 1 mg. in 0.2 cc. of saline daily for 14 days, sterile abscesses are formed in the subconjunctival space.

3. Intracorneal and intravitreal injections of cortisone leave the media cloudy.

4. Cortisone does not appear to have any effect on the regeneration of standard corneal abrasion.

5. Cortisone does not decrease the tensile strength of experimentally produced standard penetrating corneal incisions.

6. Microscopic examination of penetrating corneal lesions reveals only a slight delay in fibroblastic proliferation.

Other opinions regarding the influence of cortisone on various ocular disease are more controversial. Hobbs [99] describes a typical case of scleromalacia perforans in which cortisone was used locally and systemically, with benefit. Stark [100] finds it of value in clearing most types of keratitis, including metaherpetic inflammations, interstitial keratitis, and rosacea keratitis. Laval [101] has found that hydrocortisone may be more efficacious than cortisone when used topically in certain cases, and he points out that hydrocortisone may also be used topically in conjunction with systemic cortisone therapy.

Gordon [102] reports that hydrocortisone acetate is inferior to the free alcohol form of hydrocortisone in the treatment of ocular disease by subconjunctival injections. He recommends that the ideal treatment schedule in any severe intraocular inflammation, especially of the posterior segment, consists of an initial course of systemic therapy (oral or intramuscular), followed by subconjunctival, and then topical, therapy. His conclusions are based on a large experience at the New York Hospital. Gordon believes that approximately 60 mg. daily is a good maintenance dose in chronic cases.

Chloresium. — Lebensohn [103] supplements the experimental data of Cole and Hughes, in which Chloresium (water-soluble chlorophyll derivatives) ointment was shown to have a favorable effect in healing abraded corneas in rabbits. He has used Chloresium solution since 1946 for various types of sluggish corneal ulcers, with gratifying results. It induced epithelization after failure of other remedies in corneal ulcers incident to the keratopathy of absolute glaucoma, in ulcers of trachoma, in metaherpetic ulcers, in epidemic keratoconjunctivitis, and in ulcus serpens, after control of the infection. Chloresium solution (plain) contains purified water-soluble derivatives of chlorophyll A in a suitably buffered isotonic saline solution. It is stable and produces no irritation. A drop in the affected eye every two or three hours is recommended, followed by hot applications.

Lysozyme.—Lebensohn [103] also discusses the use of lysozyme and mentions his previous experiences with the use of egg white (containing lysozyme) dissolved in an equal amount of isotonic saline. This solution is alleged to contain lysozyme in the same titer as human tears, and 6% protein in almost the same concentration as that of plasma. The author's project was abandoned because a deleterious action was soon apparent, which he thought was due to a mucolytic action of lysozyme on corneal polysaccharides. He has, however, used the preparation with success in some cases of keratoconjunctivitis sicca, not adequately benefited by methylcellulose drops.

Irgapyrin.—By mixing equal parts of aminopyrine (Pyramidon) and 30% phenylbutazone (Butazolidin), a new compound, Irgapyrin, is obtained, which can be administered parenterally. Franceschetti and Habegger [104] find it of great benefit in irritative ocular diseases of various origins. It has a therapeutic effect similar to that of cortisone, but is less expensive, and it does not present the dangers of treatment with cortisone. It is indicated in all cases of acute inflammatory ocular disease in which the etiology is not established with certainty, especially where a tuberculous origin is probable.

Naphazoline-Sulfathiazole Emulsion. — In Poland, this substance represents the first

form of treatment for phlyctenular disease. It is a combination of a vasoconstrictor, naphazoline U. S. P. (Privine), with a mild anti-infective and antiallergenic agent, sulfathiazole (Cibazol). Good results are reported by Morawiecki.[105]

Nicotinic Acid. — Theoretically, nicotinic acid is an essential respiratory enzyme, and in its amide form it is an important link in various metabolic processes. Agarwal and Datt [106] made a clinical investigation of the effect of nicotinic acid on the healing of corneal ulcers. They studied 57 cases of various types of keratitis, using 20 of the cases as controls. Twenty of the patients were given 50 mg. of nicotinic acid daily intramuscularly, and 17 others were given 25 mg. subconjunctivally on alternate days in addition to the routine treatment. The authors feel that this treatment was of definite value. It is of interest that, in spite of rapid healing, congestion in the treated cases persisted longer than in the nontreated cases. This, they believe, is due to the vasodilative effect of nicotinic acid.

Fibrin Film.—Weisser [107] reports on the use of Fibrin Film in the treatment of 100 cases of corneal lesions of various types. The material used was a combination of thrombin U. S. P., 5,000 units, and normal human plasma U. S. P., 2.5 cc. A drop of each of these agents applied to the cornea supplies a clot of Fibrin Film which covers the damaged or diseased area, relieves pain, and, according to the author, permits rapid healing even without bandage. The author uses it in combination with antibiotics. He speculates that Fibrin Film may contain antibodies which would be of some value in treating ulcers due to infection.

Levy || has confirmed Weisser's observations but thinks that the Fibrin Film treatment will be unsuccessful if it is not carried out with meticulous detail. Levy further outlines in detail his particular technique for the application of Fibrin Film. Beneficial results have also been reported by Thorpe ¶ in the treatment of ulcerative keratitis and in a few cases of epidemic keratoconjunctivitis. He claims that it has been of definite benefit in one-third of his cases with chronic ulcerative keratitis. Tassman # has used the same material for the past eight years and has demonstrated both experimentally and clinically the adhesive and healing properties of this substance. He is most enthusiastic about its use.

Gauldi [108] has found that corneal wounds in rabbits healed without complication, and with less local reaction, when autoplasm and calcium chloride were used than when the wounds were sutured.

Ultrasound Therapy.—On the normal eye, Kleifeld [109] found that ultrasound therapy produced corneal edema and mydriasis. In other cases it relieved intractable pain. He also noted some improvement in three cases of vitreous hemorrhage.

SURGICAL THERAPY

Keratoplasty.—The literature on keratoplasty and allied subjects is as large as ever. Lamellar keratoplasty occupies an increasingly prominent position in the total literature on these subjects. The indications and contraindications of keratoplasty are well outlined by Salleras,[110] who reports the results of 172 keratoplasties done by him. He gives the indications for various types of operations and believes that no operation should be performed if vision is better than 6/60. The importance of accurate coaptation of host and donor cornea is stressed, and it is his belief that a penetrating graft of more than 8 mm. is never indicated. Lamellar grafts have the advantage that the operation is safer and that the postoperative course is much shorter, but lamellar grafts do become infected and necrotic more easily. Salleras [111] also gives his ideas of preoperative medication and introduces a hypnotic drug called Ampliactil (chlorpromazine) to obtain what he calls a "pharmacological lobotomy."

The matter of technique quite naturally occupies an important part in the minds of ophthalmic surgeons. Lister, Philps, and

|| Levy, I., in discussion on Weisser.[107]

¶ Thorpe, H. E., in discussion on Weisser.[107]

Tassman, I. S., in discussion on Weisser.[107]

Langham [112] describe a new instrument, consisting of an attachment for the slit lamp, which measures the corneal thickness accurately. This reduces some of the complications of keratoplasty which come about through differences in thickness of the host and the donor cornea. Samuels [113] gives an excellent pathological demonstration of the elasticity of Descemet's membrane. The retraction of Descemet's membrane depends a great deal upon the obliquity of the cut through it. A long incision through it increases the possibility of incomplete closure of the posterior part of a corneal incision, and Samuels points out that superficially placed sutures tend to produce gaping of the posterior half of the wound. Michaelson [114] notes the importance of holding the corneal trephine exactly perpendicular to the cornea. When an anterior synechia must be included in the trephination, the first penetration of the trephine should be over the synechia. This gives greater protection to the lens, and the cut made by scissors can be made more safely in clear than in opaque cornea. The relationship between corneal graft fixation and astigmatism is emphasized by Philps and Fincham.[115] These authors present a modification of Amsler's photokeratoscope for recording the form of the cornea by photographing its reflected image. Great emphasis is placed on exact apposition of the edges of the graft and the host cornea. They advocate the use of a small splint 12 mm. in diameter, with a thickness of 0.5 mm., which produces an immediate watertight joint between the two. Schreck [116] describes an instrument which facilitates the corneal trephining. With his instrument, the anterior chamber is kept filled with fluid injected through a separate small cannula introduced at the limbus.

The mechanism of vascularization of corneal grafts is the subject of a biomicroscopic study of 16 patients by Boudet.[117] All these had penetrating corneal grafts which became more or less opaque and vascularized. The author found new vessel formation in the deeper layers of the graft in almost all cases and practically complete absence of blood vessels in the superficial layers of the graft. He explains these findings on the basis of greater corneal edema in the posterior part of the graft than in the anterior part.

Kok-van Alphen [118] reports on a four-year study concerning problems of corneal transplantation, such as the ingrowth of the transplant, the part played by the cornea of the host, and the question as to whether or not the graft is replaced by elements of the host's cornea. Experiments were performed on rabbits in which keratoplasty was done with tissues other than cornea, namely, sclera, oral mucous membrane, and skin. Homografts of sclera were transplanted in the host's cornea. These remained quiet for 10 to 18 days and were followed by a marked irritation of the eye, with abundant vascularization of the transplant and iritis. The inflammation lasted 3 to 4 weeks; but after 3 to 4 months the transplant again cleared at the edges, and 9 to 14 months after the keratoplasty the scleral tissue appeared to be changed grossly into an opaque tissue that microscopically showed a cornea-like stroma with layers arranged in untidy fashion, such as is seen in opaque corneas. Autografts and homografts with "heterotropic tissues," viz., mucous membrane and skin, behaved practically the same as sclera during the first week following operation. Hair continued to grow in the case of skin transplants, and even nine months after operation remnants of hair could still be found microscopically. When both skin and mucous membrane were transplanted, the edges showed definite clearing at the end of four months, as though the host's cornea influenced the transplant. Microscopically there was progressive formation of a more or less clear lamellar structure, accompanied by a number of young keratoblast-like cells. The transplant became covered with an epithelium similar to that of the host. A Descemet membrane, looking very "real," with some endothelium, was present. Microscopic study suggested that the keratoblasts may originate from epithelium, from the walls of the blood vessels, and from the stroma of the host's cornea. From his summary, it appears that homografts of sclera and autografts and homografts of mucous

membrane and skin can be accepted by the rabbit's cornea. During a limited period these tissues seem to retain their individuality, but after some time they tend to become changed into a cornea-like tissue, with layers strongly resembling those of the cornea.

Further histological examinations of the changes occurring in the cornea of the host and the donor are reported by Krwawicz, Seidler-Dymitrowska, and Vorbrodt.[119] They claim to have demonstrated mitosis in the corneal cells of the transplant 10 days after operation, proving vitality of these corneal cells. They also confirm Filatov's idea that the corneal cells have histiocytic properties.

Further experimental grafting is reported by Sie-Boen-Lain,[120] who grafted full-thickness discs of sclera into the cornea of the same rabbit. These grafts seemed to undergo some clearing. Lamellar scleral grafts placed either in the cornea or into the anterior chamber remained opaque.

Lamellar Keratoplasty in Treatment of Ocular Tumors and Inflammation.—Lamellar keratoplasty seems especially useful after radical excision of tumors of the limbus. Friede[121] reports such an operation for an extensive dermoid of the limbus. He claims that the cosmetic results are better than those after simple excision, when a prominent corneal scar usually develops. Friede[122] recommends radical removal of all tumors of the limbus by lamellar keratectomy and sclerectomy down to the level of Descemet's membrane, after which a lamellar graft is sewed in place. Several successfully treated cases are reported.

Paufique and Moreau[123] describe an unusual treatment for scleromalacia perforans in which by a special technique they accomplished with a scleral transplant a good result. Their histological examination of the excised sclera indicated localized scleral degeneration, and the authors believe that the disease is neither an infectious process nor a rheumatoid nodule.

Keratoplasty for Keratoconus.—The literature on this subject has been rather sparse during the last year. Eight cases of lamellar keratoplasty are reported by de Rezende,[124] who urges extreme precaution in the protection of Descemet's membrane. Sato and Komori[125] describe posterior incision of the cornea for the treatment of cornical cornea, myopia, and astigmatism. They report the histological changes which occur after such treatment. Immediately after the incision there is considerable retraction of the cut edges of Descemet's membrane and edema of the cornea immediately begins. They state that cellular infiltration never occurs in the stroma throughout the course of the inflammation, and there is perfect recovery of corneal transparency. In the course of three weeks an "endothelial connective tissue" fills up the gap in a spindle form. The cut edges of Descemet's membrane never heal.

Preservation of Cornea for Keratoplasties and Related Subjects.—Salleras,[126] who has had a large experience in these matters, recommends that the enucleated eye be placed in a vial with saline solution, irrigated with penicillin solution, and kept at 2 C. He points out that much better results are obtained by using fresh donor material, even though enucleated eyes may be preserved in a refrigerator for 10 days. In his experience the corneas from older persons are better than those from a fetus because of their better curvature and more normal thickness.

Orzalesi and Ciuffo[127] carefully review present-day concepts of the mechanism of clouding of corneal grafts after keratoplasty and the changes which occur in corneal tissue during storage. These authors find histamine-like substances in the tissues, which upon intracutaneous injection cause increased capillary permeability and leucocytic exudation. They conclude that the clouding of the graft after keratoplasty is probably an allergic phenomenon.

Corneal Alloplasty.—Salleras[126] reviews the experimental work done in substituting some type of plastic material for the cornea and concludes that all such grafts are extruded sooner or later. Nevertheless, Sommer[128] reports four attempts in humans to replace cloudy corneas with a glass window where regular keratoplasty had failed. In the

fourth patient the glass window remained in place for eight months after the operation.

Surgical Treatment of Xerosis.—Filatov's ingenious operation for lacrimal deficiency consists in transplanting the parotid duct in the conjunctival sac. A successful result of such an operation is described by Arkin and Dryjski,[129] who employed it in a patient with bilateral corneal xerosis. The authors state that the result was satisfactory except for a very annoying watering of the eye during ingestion of food.

PTERYGIUM

The subject of the pterygium continues to occupy the attention of ophthalmologists wherever their specialty is practiced. Amsler [130] describes its effect on corneal astigmatism and demonstrates it photographically by using the Placido disc. The astigmatism appears to be caused by traction on the cornea, which occurs early in the course of the pterygium, and hence early surgical removal is recommended. An appealing surgical procedure is described by Gonzales Vanrell,[131] who in 10 cases of pterygium did the following operation: The pterygium was completely excised, and the raw surface was then covered with a quadrangular flap of conjunctiva excised from the superior temporal quadrant of the same globe. The conjunctival graft was sewed in position with fine silk sutures. He reports excellent results. Friede [132] recommends a prophylactic trephining, and he removes a 1 mm. disc of one-half the corneal thickness just at the progressive edge. The defect is allowed to heal by itself. For more advanced pterygia he does a keratectomy and applies a triangular lamellar corneal graft to the bared sclera.

Rosenthal [133] presents an excellent chronological review of pterygium therapy as his thesis submitted at the University of Pennsylvania, with what appears to be a complete bibliography on the subject. The past history and present status of the pterygium are well summarized in his last three paragraphs.

> Down through history there have been many who have practiced and reported upon various operative techniques without making any outstanding contributions. They number in the hundreds and their names may be found in the literature of all nations and all ages. And so it appears that for about 30 centuries man has tried to conquer this little growth called pterygium.
>
> It has been incised, removed, split, transplanted, excised, cauterized, grafted, inverted, galvanized, heated, dessicated, rotated, coagulated, repositioned, and irradiated.
>
> It has been analyzed statistically, geographically, etiologically, microscopically and chemically—yet it grows onward primarily and secondarily. We look with interest to its future.[135]

SUPPLEMENT

In writing this review, I have taken full cognizance of my limitations. The literature is vast and in all languages. I have cited extensively from original articles, as well as from the excellent abstracts done by other reviewers without giving individual credit where it is due. I am grateful for this assistance.

Doubtless many articles have been omitted; others have been merely named in the list of references. It is hoped that the emphasis has been rightly placed.

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Special Report

THIRD INTERIM MEETING OF PAN-AMERICAN CONGRESS OF OPHTHALMOLOGY

IN SÃO PAULO the curtain is long down on a successful experiment in international relations, the Pan-American Congress of Ophthalmology. The memoranda, the files of correspondence, all the paraphenalia and trappings which accumulate during the planning of such a meeting are cleared away, and, we hope, our Paulistano hosts rest easily in the satisfaction of a job well done. As for the guests; home again, the vicissitudes of travel, the hurtling, as it were overnight, into a distant land with different customs and unfamiliar tongue, the headaches and alimentary distress which seem so inevitably a part of rapid transit and rare entertainment, all these tribulations fade into insignificance in the after-glow of a warm enthusiasm for our South American friends and their country.

From North America we came by boat and plane, some 35 or 40 strong, some with wives, some with children, two bachelors, rendezvousing in Rio at the fabled Cocacabana Grand Hotel, now somewhat subdued, its gaming tables prohibited. From here we diverged momentarily on individual pleasure jaunts day and night, in accordance with age and taste. By day Rio, its crescent beach lined with gorgeous hotels, splendid apartments, and pretentious residences, the wide harbor with Sugarloaf and Hunchback on the wings, the parks and boulevards, this blend of natural beauty and modern architecture, is incomparably magnificent. By night, in the more intimate environment of the night clubs, the scenery, while more familiar, was by no means unappreciated. From Rio we flew as a group to São Paulo, being met at the airport by Miss Jean Sykes, Dr. Alvaro's most competent secretary. How relieved she must have been to see in the flesh and to be able to count the heads of so many of the participants in the program. The Commodoro Hotel, modern, quiet, and comfortable, served as headquarters for our group.

Our Pan-American Congress officially opened on the night of June 11, with the usual addresses of welcome by the dignitaries and authorities. Preceding the invocation, cocktails were served on the upper floor and roof garden of the São Paulo Medical Association Building. This party was held conjointly with the Brazilian Congress of Ophthalmology and the International Congress of Oto-Neuro-Ophthalmology, participants in the grand program. Graced by the presence of the perennially young and irrepressible Arruga and a score of other European luminaries, including Safar, Franceschetti, Mueller, Desvignes, Grozzano, and Arslan, we were soon aware that this meeting was to be a far cry from a limited Pan-American Congress, and so it proved. This multilingual and highly vocal group rapidly developed the atmosphere of a modern tower of Babel, in which we North Americans were very completely *de trop*.

The morning which followed these festivities, Saturday, the 12th, had with rare foresight been left free, provisions being made, however, for a visit to hospitals, where surgical demonstrations had been arranged. Possibly because of the necessity of an early breakfast, the clinics were not widely attended by the American group. Dr. Ray Dailey, with her customary initiative and enthusiasm, made the necessary connections and reports that the two surgical clinics conducted at the two medical

schools were most interesting and instructive. Dr. Arruga and Dr. Safar operated at the Rezende Clinic. Dr. Alvaro and associates operated at his clinic and after the surgery entertained the visitors at a very elaborate coffee.

The scientific program was sponsored by the three organizations: the Pan-American Congress of Ophthalmology, the International Congress of Oto-Neuro-Ophthalmology, and the Brazilian Congress of Ophthalmology. The program got underway on Saturday, June 9, and closed on Thursday, June 17. The major subjects in which the three organizations participated were (1) Prevention of Blindness, (2) Uveitis, (3) Therapeutic Advances, (4) Metabolic Disturbances, (5) Keratoplasty, (6) Avitaminotic Disturbances, and (7) Physiopathology of the Facial Nerve. The mornings were reserved for the essayists, who were held strictly within an allotted period of 12 minutes for the presentation of a particular subdivision of the official subject. Arrangement, timing, and execution deserve especial commendation. The programs began promptly and moved smoothly and unhurriedly along, a sense of continuity developing as each participant became the presiding officer for the following paper. Each paper as presented was simultaneously translated into Portuguese, Spanish, and English and was broadcast to minature radio receiving sets and earphones provided individually to each of the audience—a notable advance in convenience and comfort over the plug-in receiver. All comment was reserved for the afternoon sessions, at which time one had the choice of participating in a discussion of the morning papers, interviewing the essayists, or viewing moving-picture presentations of operative procedures.

The opening assignment on Saturday morning related to the prevention of blindness and was highlighted by Dr. Franklin Foote's paper on "Definitions of Blindness." The afternoon session was reserved for free papers. The night session, under the sponsorship of the Brazilian Congress, was devoted to a discussion of uveitis. After a day of diversified social activities on Sunday, the scientific program on Monday was devoted to a review of Recent Advances in the Treatment of Eye Diseases. Participants in this symposium were enlisted from all parts of the Americas. Some 15 subjects were assigned. Each anatomical subdivision of the ocular system, in the customary order, came under consideration, beginning with advances in therapy in diseases of the orbit and closing with a discussion of the therapy of optic neuritis. Tuesday morning was reserved for four papers on "Metabolic Disturbances in Oto-Neuro-Ophthalmology" under the auspices of the International Congress of Oto-Neuro-Ophthalmology. The afternoon was reserved for free papers, movies, and interviews. On Wednesday the assignment was to the Brazilian Congress of Ophthalmology. The official subject was "Keratoplasty." Four very excellent papers were presented on this subject. Later in the morning there were papers dealing with the prevention of blindness by the Mesdames Harry Gradle, Dorothy Bryan, and Ben Gray. Thursday's program related to the "Physiopathology of the Facial Nerve." The major subjects under discussion, considering the definitive limitations assigned, were handled by the essayists with credit to themselves and presumably to the satisfaction of the audience, which, considering the barriers of language and the technical difficulties of translation and broadcasting, was remarkably attentive.

The social program added greatly to the pleasure and general educational value of the meeting. First of all, there is São Paulo—a truly fabulous city, with growth so rapid as to have outdistanced its own publicity. As we come in by plane, the first view and impression contrast sharply with the appearance of our smoke-shrouded and soot-encrusted cities. As the plane turns for landing, through a

smokeless, crystal-clear atmosphere, the towering skyscrapers stand stark and clean, in parallel panels, gleaming in the sun against the ever-green blanket of tropical growth. The thoroughfares, traverses, parkways with the smoothly flowing traffic, are easily recognized signs of orderly planning and progress. The skeletons of numerous unfinished buildings, stretching up to the already impressive skyline, epitomize the great surge of development that makes this little-heard-of city the coming metropolis of South America. Within the city the tempo is unhurried: one notes the orderly queuing-up for buses, the remarkable performances of taxis of every vintage, the courteous, friendly, and dignified service in the elevators and dining rooms. The food, excellent everywhere, was impressive in the restraint of the billing.

The program was so arranged that free time was available for exploring the city and for excursions to Santos and Campinas. For those of sedentary nature with sporting inclination the sumptious Jockey Club was made available. Some of our group preferred *futebol* (soccer). This is the national sport of all South America. Unfortunately for us, the big-league teams were in Switzerland competing in international matches. We were spectators at a game between local rivals. The match was played in the large, well-appointed municipal stadium of Pacembu before 70,000 partisans, whose enthusiasm is such that in comparison the most rabid North American college spectator becomes a mere Casper Milquetoast. Particularly colorful were the salvos of fireworks which greeted the home team as they entered the playing field. These firecrackers and miniature Roman candles apparently were fired with utter disregard to the safety of surrounding spectators. This must have been a trying time for any of the Society for the Prevention of Blindness who might have been present. The tour of the city was highlighted by a visit to the Butartã snake farm and venom institute, where antivenom is prepared for protection against not only the snakes of the Amazon, but all South American venomous reptiles and insects. This is an unexpectedly large institute, with several modern, well-appointed buildings which housed the various laboratories.

All who spent the Sunday in Santos thought this the most interesting social event of the Congress. Santos is the seaport city of São Paulo. There was, first, the exciting cable car ride down the mountain. We were met by Dr. Gino Berretini and his associates, who deserve special credit for the inter-American and international fellowship created in the tour of the Santos Hospital (Bercario da Santa Casa de Santos), the exotic barbecued beef dinner and afternoon at the Santos Medical Society, and the tour of the Santos beaches, including the boat ride to the private "Fishing Island" Club. For those who elected the Campinas excursion opportunity was afforded to visit a large *fazenda*, or coffee plantation, where a bountiful luncheon was provided and where the intricacies of growing, preparing, and marketing coffee were demonstrated. Coffee seems to be as intricately bound into the economy of this part of Brazil as does tobacco to the southeastern section of our country. Fortunately for our Paulistino friends, no one has as yet discovered a carcinogenic factor in coffee.

Private dinner parties were the order for Sunday and Monday nights. On Tuesday night the Congress was entertained at a large "Barn Dance," attended by all who were still in circulation. This was an extravaganza in the Latin American mood. There was a tremendous crowd, with continuous rumba orchestra and great conviviality stretching well into the small hours. Needless to say, there was food and drink for those able and interested. For most of the North American group the party ended with the banquet Wednesday night—an evening sharply in

constrast to the preceding one—a somewhat ponderous affair, prolonged by the greetings and felicitations of some representatives of the various countries attending the combined meeting.

And so we take leave, flying back across the Amazon jungle, over the Andes and the high plateau of Peru. With us we carry these impressions: Brazil, a gigantic, sprawling nation, whose tremendous resources are little appreciated by the average North American; São Paulo, a fascinating city, incredible in its growth, in its orderly confusion as the new replaces the old, and in the controlled urgency which one senses in the early street noises of the awakening city and in the perpendicular rows of late-burning lights which illuminate the façades of the tall office buildings; Paulistanos, an ebullient, energetic people with a love for work and a zest for living; the Congress, a remarkable example of cooperation and coordination by the three participating societies; our hosts, considerate, hospitable, gracious, and forgiving. To Dr. Alvaro and all those who made this meeting so pleasant and so worth while, in the official languages of the Congress; in Portuguese, *obrigado*; in Spanish, *gracias*; in English, we thank you.

CORRECTION

Owing to a typographical error in the copy submitted, the date of the Fifth Pan-American Congress of Ophthalmology was erroneously given (December issue, page 975) as Jan. 9 to 14, 1955. This Congress will meet in Santiago, Chile, Jan. 9 to 14, 1956.

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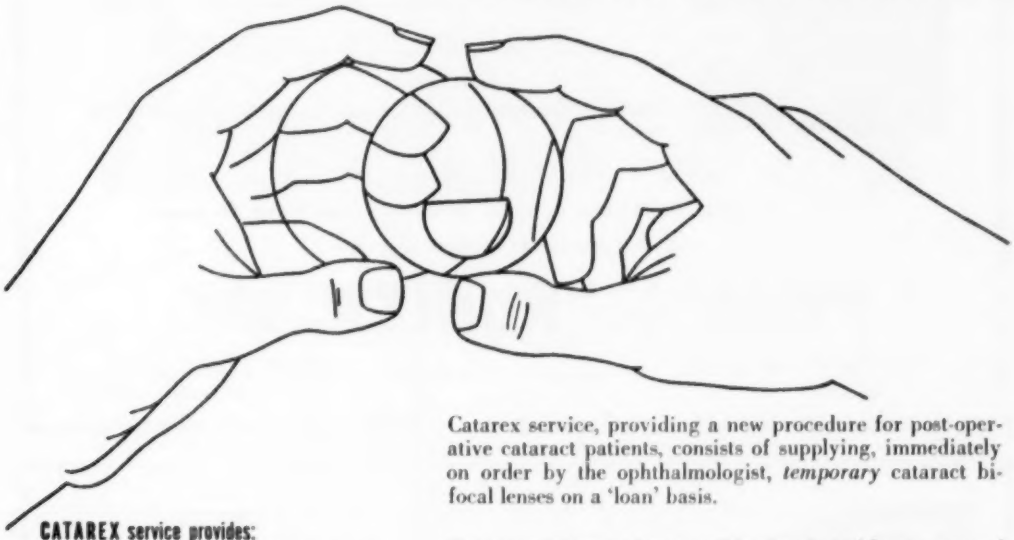

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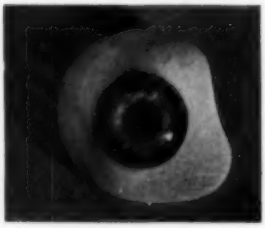

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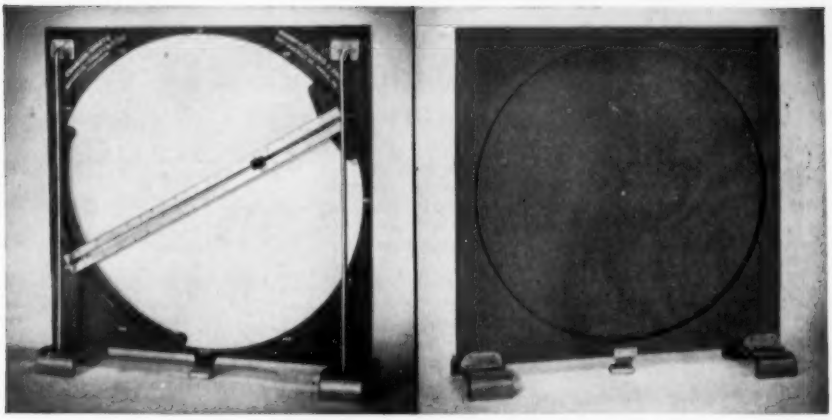

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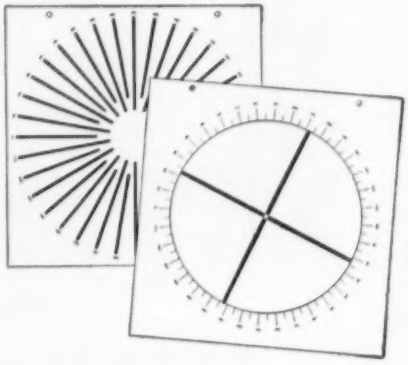

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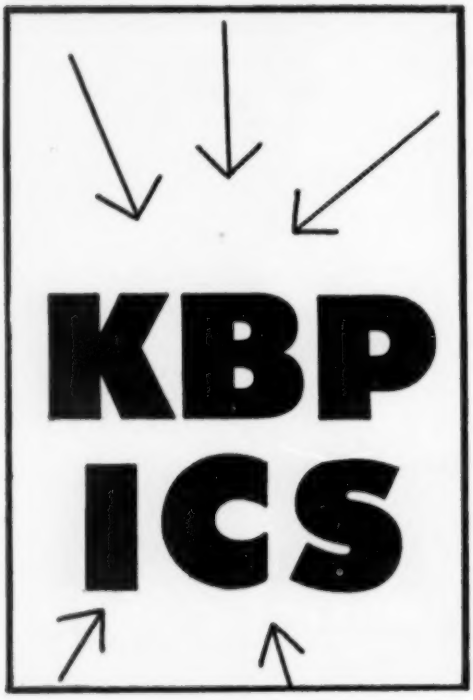

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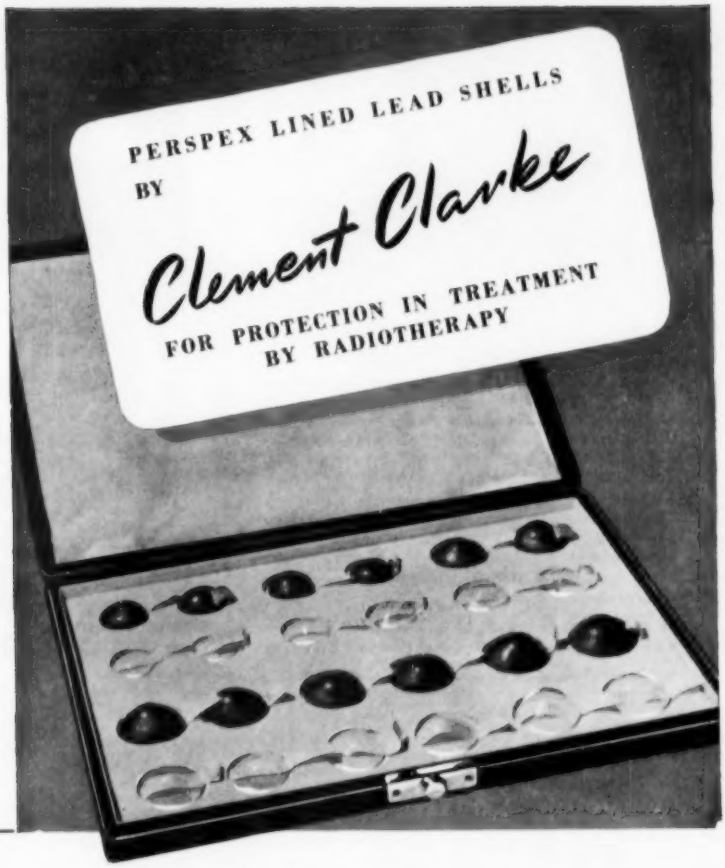

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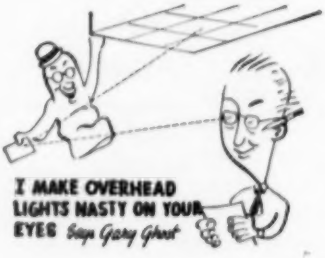

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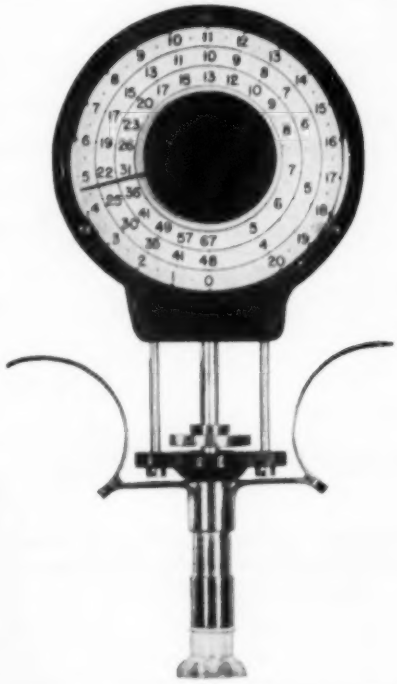

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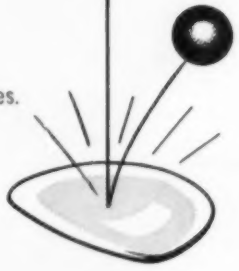

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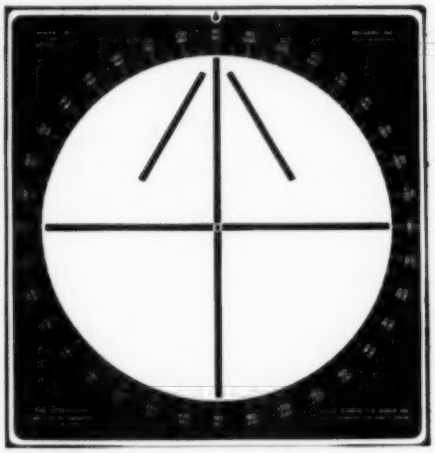

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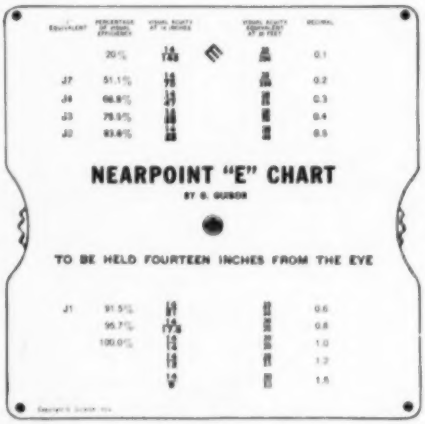

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